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A FURTHER REPORT ON THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE BY INTRAMUSCULAR INJECTIONS, SUBCUTANEOUS IMPLANTATION OF PELLETS, AND SUBLINGUAL ADMINISTRATION *

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SINCE the original reports by Levy-Simpson [1] and Thorn [2, 3, 4] on the use of desoxycorticosterone acetate in the treatment of Addison's disease, many further reports have appeared confirming its value and pointing out its limitations and toxic effects resulting from overdosage.[5, 6, 7] In 1939 an advance in therapy was made by Thorn and his co-workers [8, 9] who utilized the technic of Deanesly and Parkes [10] and maintained adrenalectomized dogs and patients with Addison's disease in good condition by implantation of pellets of crystalline desoxycorticosterone acetate subcutaneously. By this method a slow and steady release of hormone, calculated at about 0.2 to 0.3 mg. a day per pellet, could be effected, the pellets being of such a size as to last about one year. Since then others have reported their experience with pellet implantation,[11, 12, 13] and more recently Thorn has reviewed his experience with a large series of cases.[14, 15] In 1940 Anderson and co-workers [16] reported the successful use of a preparation of desoxycorticosterone acetate dissolved in propylene glycol and administered sublingually. These results were later confirmed by Turnoff and Rowntree.[17]

The treatment of Addison's disease by the older methods was not attended by any serious effects from overdosage of cortical extract. It soon became apparent, however, that desoxycorticosterone acetate was an extremely potent hormone and, when injudiciously employed, hazardous. As with the old cortical extract it did not represent complete replacement therapy.

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Alarming hypertension, excessive retention of salt and water with peripheral and pulmonary edema and cardiac failure were reported with increasing frequency and several patients died as a result of this.[5, 11, 12, 14, 15, 18] Overdosage was also noted to be associated with other manifestations which sometimes were difficult to distinguish from incipient adrenal insufficiency. Among these may be mentioned anorexia, headache, and muscular weakness. The Mayo Clinic group [19, 20] pointed out the dangers of restriction of potassium in patients receiving desoxycorticosterone acetate, and, in fact, suggest that the administration of potassium may be of value in patients manifesting toxic symptoms. Thorn [14] described the occurrence of marked muscular weakness and transient paralysis in a patient receiving the synthetic hormone. The serum potassium was very low, and relief was achieved by administering potassium. A similar phenomenon was noted in dogs by Kuhlmann et al.[21]

From the beginning it has been clear that desoxycorticosterone acetate has little effect on the disturbance in carbohydrate metabolism in Addison's disease, and in this respect does not represent complete replacement therapy.[4, 12, 14, 19, 22, 23] The danger of hypoglycemia and of possible sudden death from this during treatment with the synthetic hormone has been repeatedly pointed out. That other functions of the adrenal cortex may not be possessed by desoxycorticosterone acetate is suggested by the work of Ingle [24] who showed that, although desoxycorticosterone acetate was the most potent life-maintaining factor in adrenalectomized rats, it did not exert as potent an effect on the muscle work capacity of the rats as some of the other crystalline factors.

Thus, although therapy with desoxycorticosterone acetate represents a real advance in therapy, its incautious use may be associated with real dangers, and its effectiveness is limited by the fact that it does not represent complete replacement therapy.

Results

In a previous publication [12] we reported our experiences with desoxycorticosterone acetate in the treatment of five patients with Addison's disease. Four of these patients received implantations of pellets. The present report deals with further observations on these four patients, some of whom have now been treated with desoxycorticosterone acetate for over two and a half years. In addition, four new patients have been added to the series. In the whole series, three are females and five are males, and their ages vary from 21 to 57 years. A tuberculous etiology is definite in three cases and probable in three others.

Case Reports

Case 1. D. G., a 23-year-old woman, whose history has been given in detail before,[12] had 10 pellets of crystalline desoxycorticosterone acetate implanted subcutaneously on September 16, 1939. The average weight of each pellet was 128 mg.

and the total dosage was calculated to yield approximately 3 mg. per day, which is equivalent to about 5 mg. a day when given intramuscularly. At this time she was receiving no supplementary salt by mouth. Two months after implantation of pellets the blood pressure had risen to 150 mm. Hg systolic and 95 mm. diastolic, and on slight exertion would rise to 180 mm. systolic and 110 mm. diastolic, which was associated with dyspnea and cardiac palpitation. Her weight was 122 pounds (55 kg) as compared to 104 pounds (47 kg.) prior to therapy with desoxycorticosterone acetate. Blood electrolytes were entirely normal. For this reason she was readmitted to the hospital (November 10, 1939 to December 3, 1939) for restudy and for removal of pellets. A low salt diet yielding approximately 3 gm. of sodium chloride a day had no effect on the blood pressure. On November 22 an area of fluctuation appeared at the lower end of the scar and two fragmented pellets were extruded. Following this, there was no appreciable change in blood pressure or weight. On December 3 a third pellet weighing 91.8 mg. was removed. This represented a loss of 36 mg. in weight of the pellets in the course of 77 days, or 0.46 mg. a day. At this time the blood sodium was 133.1 milli-equivalents/L., the chloride 108 m.e./L., and the potassium 6.9 m.e./L. On December 11 the blood pressure was still 160 mm. Hg systolic over 100 mm. diastolic, so a fourth pellet, weighing 96.7 mg., was removed. This pellet had broken down at the rate of 0.35 mg. per day. The site of implantation still showed an area of fluctuation and a small amount of serum could be extruded. One month later her blood pressure was still elevated and her blood electrolytes were normal. Despite the persistent hypertension, she now felt subjectively well. On January 30 a fifth pellet was extruded from the area of fluctuation. This pellet weighed 64.4 mg. and represented a daily yield of 0.5 mg. Thereafter, her blood pressure fell to within normal limits, ranging between 105–125 mm. Hg systolic and 75–85 mm. diastolic; she felt extremely well and was able to resume her occupation as a bookkeeper. One month later she developed an upper respiratory infection with elevation of temperature to 102.4° F., but showed no evidences of adrenal insufficiency. At this time she was advised to resume taking 5 gm. of sodium chloride a day. Shortly thereafter her blood sodium was 137 m.e./L., chlorides 104 m.e./L.

On June 18, 1940, nine months after the original implantation, she returned to the hospital with the complaint of increasing anorexia and weakness of two weeks' duration. On admission her blood sodium was 133 m.e./L., chloride 105 m.e./L., and urea nitrogen 12 mg. per cent. Her blood pressure was 95 mm. Hg systolic and 54 mm. diastolic and weight 125 pounds (57 kg.). Two days after admission she felt much weaker and her blood pressure had fallen to 70 mm. Hg systolic and 50 mm. diastolic. Since she was now in obvious adrenal insufficiency, she was given intravenous saline in addition to 12 grams of sodium chloride by mouth. For two days she received 10 mg. of desoxycorticosterone acetate intramuscularly, then 5 mg. daily for a week, and then 2.5 mg. daily thereafter until implantation of pellets. After a week, salt was reduced to 6 gm. a day. On this régime her blood pressure rose to 110–120 mm. Hg systolic and 70–90 mm. diastolic, and weight to 130 pounds (59 kg.). On July 1 five pellets of desoxycorticosterone acetate with an average weight of 124 mg. were implanted subcutaneously. She was discharged two weeks later with a normal blood pressure and normal blood electrolytes. She weighed 128 pounds (58.2 kg.) and was taking 5 gm. of supplementary sodium chloride a day. During the subsequent few months her general condition remained excellent and she was able to indulge in full activity including working eight hours a day and partaking of moderate exercise, such as dancing. Hypoglycemic symptoms, of which she had previously occasionally complained, were avoided by taking frequent small feedings of carbohydrate when she indulged in more than usual exertion. Her blood pressure ranged between 135–150 mm. Hg systolic and 85–95 mm. diastolic, but she complained of no dyspnea, palpitation, or edema. On September 11, ten weeks after implantation,

a pellet weighing 105 mg. erupted spontaneously. This represented a breakdown rate of 0.26 mg. a day. The blood sodium at this time was 135.4 m.e./L. and chloride 111.0 m.e./L. Blood pressure was 135 mm. Hg systolic and 85 mm. diastolic. Thereafter, her course was excellent and she led an entirely normal life. Her blood pressure ranged about 125 mm. Hg systolic and 90 mm. diastolic.

On June 16, 1941, eleven and a half months after implantation, she was readmitted to the hospital complaining of decreasing appetite and strength and dyspnea on exertion, of about three weeks' duration. On admission, her blood pressure was 104 mm. Hg systolic and 70 mm. diastolic, weight 124.5 pounds (56.6 kg.), hematocrit 33 per cent, blood sodium 140.2 m.e./L., chloride 100 m.e./L., and urea nitrogen 13 mg. per cent. After five days without supplementary salt or hormone, her weight fell to 121 pounds (55 kg.), blood pressure to 96 mm. Hg systolic and 60 mm. diastolic and her hematocrit rose to 37.4 per cent, but there was no significant change in the blood electrolytes. Nevertheless, it was felt that there was sufficient evidence to suggest mild adrenal insufficiency due to exhaustion of the pellets. She was started on 6 grams of additional salt and 2 mg. of desoxycorticosterone acetate intramuscularly daily. After four days the latter was increased to 2.5 mg. a day for three days and then reduced to 2.0 mg. for the next three days. On 10 days of this régime her blood pressure rose to 120 mm. Hg systolic and 86 mm. diastolic, weight to 130 pounds (59 kg.), and the hematocrit fell to 29.2 per cent.

At this time she was started on a trial period of desoxycorticosterone acetate in propylene glycol by the sublingual route, receiving 2 mg. a day, a dose of hormone which was quite adequate by the intramuscular route. On 10 days of this therapy her weight fell to 126 pounds (57.3 kg.), her blood pressure to 102 mm. Hg systolic and 72 mm. diastolic and her hematocrit rose to 36 per cent. Subjectively she felt as well as ever during this period. At the end of this period, her blood sodium was 139.9 and chloride 106.0 m.e./L.

After being restabilized on 2.5 mg. of the hormone intramuscularly daily, four pellets of the crystalline desoxycorticosterone acetate with average weight of 125 mg. each were implanted on July 16, 1941. The blood pressure on the day of implantation was 132 mm. Hg systolic and 85 mm. diastolic. One month after implantation a single pellet erupted spontaneously. Her blood pressure was 150 mm. Hg systolic and 100 mm. diastolic, and subjectively she felt quite well.

Discussion. The untoward effects of overdosage with too many pellets which occurred on the first implantation were avoided on subsequent implantations, and the response to this type of therapy has now been excellent. The patient has been able to return to an entirely normal mode of living. The trial period with the sublingual preparation demonstrated that dose for dose this mode of administration was not as effective as the intramuscular or the pellet method.

Case 2. S. R., a 21-year-old man, previously reported as case 2, had 10 pellets of desoxycorticosterone acetate implanted subcutaneously on June 19, 1939, after having been maintained on the intramuscular preparation (5 mg. per day) for three weeks. The average weight of each pellet was 103 mg. Directly after operation he received intravenous saline for 24 hours in addition to 10 grams of salt per day. As a result of this he promptly developed headache, edema, moderate hypertension, dyspnea, a gallop rhythm. When the extra salt was reduced to 2 grams a day, these untoward manifestations disappeared and he was discharged feeling much improved. The blood electrolytes were entirely normal. Four months later, his condition was excellent and the extra salt was discontinued. His blood pressure ranged between

130–140 mm. Hg systolic and 80–90 mm. diastolic. He was able to return to work in a machine shop and as a delivery boy. Eight months after implantation his weight and blood pressure were maintained and his blood sodium was 140 m.e./L. and chloride 111.6 m.e./L.

On May 6, 1940, eleven months after implantation, he returned to the hospital because of increasing fatigue and weakness for one month. His weight was 130 pounds (60 kg.) as compared to 138 pounds (63 kg.) on discharge. His blood pressure was 120 mm. Hg systolic and 78 mm. diastolic, hematocrit 39.5 per cent, blood sodium 140.6 m.e./L., chloride 105.6 m.e./L. and urea nitrogen 7 mg. per cent. Since there was not yet conclusive evidence of exhaustion of pellets, he was discharged after several days' observation, taking 10 grams of salt daily. Under observation for the next month on this régime, he had increasing symptoms of weakness and anorexia, and his weight and blood pressure continued to fall. He was readmitted to the hospital on June 24. His weight had fallen to 124 pounds (56.4 kg.), his blood pressure to 110 mm. Hg systolic and 60 mm. diastolic; his hematocrit was 38 per cent, blood sodium 137.2 m.e./L., chloride 106 m.e./L., and urea nitrogen 8 mg. per cent. All extra salt was now discontinued for 10 days, but there was no appreciable change in his weight, blood pressure, hematocrit, or blood electrolytes during this period. The blood sodium was 135.1 m.e./L. Subjectively, however, he felt definitely worse than he did while receiving the hormone. Despite the inability to demonstrate further changes characteristic of adrenal insufficiency without using more drastic methods, it was decided to implant a small number of pellets, since his clinical condition had definitely deteriorated. Accordingly, on July 7, 1940, four pellets, weighing approximately 125 mg. each, were implanted. On the basis of previous observations it was calculated that these should yield a total of approximately 1.2 mg. a day and should last about one year, assuming a breakdown rate of about 0.3 mg. per day. He was discharged taking 5 gm. of salt a day. His weight rose to 130 pounds (60 kg.) and blood pressure to 132 mm. Hg systolic and 84 mm. diastolic.

During the subsequent 11 months of observation his condition remained very satisfactory. He worked irregularly, but otherwise led a relatively normal life. For a time he developed a distaste for salt, as compared with a craving for it prior to adequate therapy. His blood pressure ranged between 110–130 mm. Hg systolic and 70–90 mm. diastolic; his weight remained constant, as did his electrolytes.

On June 9, 1941, eleven months after implantation, he was again admitted to the hospital because of the slow and insidious development of weakness, loss of appetite, and loss of weight over a two month period. The physical examination was essentially as before, except that he now had a palpable liver. His weight was 120 pounds (54.6 kg.), hematocrit 44.5 per cent, blood pressure 90 mm. Hg systolic and 60 mm. diastolic, blood sodium 141 m.e./L., chlorides 106 m.e./L., and urea nitrogen 18 mg. per cent. There was now obvious clinical evidence of adrenal insufficiency, despite the normal blood electrolytes, and he was started on 2 mg. of desoxycorticosterone acetate intramuscularly and 6 grams of salt daily. Ten days later his weight was 127 pounds (57.7 kg.), hematocrit 37 per cent, blood pressure 130 mm. Hg systolic and 80 mm. diastolic, blood sodium 140.8 m.e./L., chloride 115.0 m.e./L., and urea nitrogen 8 mg. per cent.

A trial with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was now begun, 2 mg. being administered daily for three days and 2 mg. twice daily for three days, at which time the experiment had to be discontinued because of the development of a tooth infection. However, on this régime he lost seven pounds in weight (3.2 kg.), his hematocrit rose from 37 per cent to 40 per cent, and his blood pressure fell to 110 mm. Hg systolic and 70 mm. diastolic.

At this time he developed a toothache, for which an extraction was performed under mandibular block. Because of this he was again given the intramuscular

preparation of hormone, receiving 2 mg. a day. Three days later, trismus and some swelling in the submaxillary region were noted. Five days after the extraction his temperature suddenly rose to 103° F., and an intense brawny tender swelling developed on the entire left side of the neck, together with increased trismus, dysphagia, and glottal edema. Intravenous glucose in normal saline was administered, and the dose of desoxycorticosterone acetate was increased to 5 mg. a day, and then to 5 mg. twice a day during the acute illness. Frequent blood pressure determinations were made, and the hematocrit was determined daily. Since nothing could be taken by mouth, glucose in saline was administered intravenously continuously. On the second day his temperature had risen to 105.4° F.; he responded poorly and was desperately ill. Chemotherapy with sulfathiazole intravenously was begun, but had to be discontinued on the fourth day because of the development of purpura due to thrombocytopenia. Fortunately, at this time improvement began to set in. During the acute febrile phase of the illness, which lasted six days, the hematocrit fell from 40 per cent to 30 per cent; the blood pressure ranged between 116 mm. Hg systolic and 90 mm. diastolic and 150 mm. systolic and 85 mm. diastolic; his weight rose from 118 to 120 pounds (53.7 to 54.6 kg.); the blood sodium was 144.4 m.e./L., the chloride 115.0 m.e./L., and urea nitrogen 8 mg. per cent during the height of the illness. At no time was more than 10 mg. of desoxycorticosterone acetate given, and the salt intake varied between 10 and 19 grams a day.

Following this acute illness there was a definite increase in the patient's requirement for hormone as compared with the period prior to it. On 3 mg. a day and 6 grams of salt he lost three pounds in weight and his hematocrit rose to 35 per cent during the first week after the acute illness, but thereafter he slowly regained weight and strength and his blood pressure averaged about 130 mm. Hg systolic and 85 mm. diastolic. He was discharged on July 27 with normal electrolytes, and weighing 122 pounds (35.5 kg.), after having been taught to administer the hormone himself. He was readmitted on August 18. His weight was 125 pounds (56.9 kg.), and the blood pressure was 132 mm. Hg systolic and 90 mm. diastolic. His general condition was definitely improved. He was then maintained on 2.5 mg. and 6 grams of salt daily until implantation of four pellets, with an average weight of 125 mg., was performed on August 25. During the subsequent month of observation, his condition remained satisfactory.

It is interesting to note that this patient, who was the first to be implanted at this hospital and who originally received more pellets than he required, as was apparent from subsequent observations, did not develop serious toxic manifestations. Except for the brief period postoperatively, when he received an excessive amount of saline intravenously and developed transient hypertension and edema, he was very well during the first year.

No definite conclusions can be drawn concerning the value of the sublingual preparation in this case because of the complicating severe infection. In the management of the patient during this serious complication it should be emphasized that a relatively small amount of desoxycorticosterone acetate, 5 to 10 mg. a day, was necessary to prevent the development of crisis, and that by careful check on the salt balance, edema and hypertension were avoided. The increased requirement for hormone after a severe infection has been frequently noted before.

Case 3. J. S., a 47-year-old man, previously reported as case 3, had 13 pellets of desoxycorticosterone acetate implanted subcutaneously on July 31, 1939, two

months after he came under our observation. For one month prior to implantation, he had been receiving 5 mg. of the synthetic hormone intramuscularly and 10 grams of salt by mouth daily. Although on this régime the blood sodium and chloride, blood pressure and weight had increased, and the hematocrit and blood potassium had decreased, his clinical improvement had not been proportionately as striking and he continued to complain of weakness and anorexia. After implantation of pellets his strength and appetite improved slightly, but he now began to complain of precordial pain on slight exertion which was typically anginal in character and was relieved by nitroglycerin. His blood pressure was found to range between 150–185 mm. Hg systolic and 80–98 mm. diastolic. Since these symptoms were not relieved by discontinuing extra salt by mouth, four pellets were removed surgically on September 26. One month later the patient's blood pressure was 145 mm. Hg systolic and 88 mm. diastolic and his weight 121 pounds (55 kg.), but he continued to complain of angina which incapacitated him as much as his Addison's disease had previously done. During the following three and a half months there was no appreciable change in his clinical status, and his blood pressure was found to be approximately 160 mm. Hg systolic and 100 mm. diastolic. He was readmitted to the hospital on January 15, 1940. During the month prior to admission he had lost 10 pounds in weight and his appetite had been poor. His blood pressure was 160 mm. Hg systolic and 94 mm. diastolic, hematocrit 44 per cent, blood chlorides 106 m.e./L., sodium 145 m.e./L., urea nitrogen 20 mg. per cent, and sugar 55 mg. per cent. The venous pressure and circulation time were normal and there were no clinical evidences of cardiac failure. The electrocardiogram showed no abnormality. Fundal examination revealed incipient retinal arteriolar sclerosis. Another glucose tolerance test again showed a flat curve. Under observation he had several episodes of precordial pain uninfluenced by placebos but relieved by nitroglycerin. On January 24, four pellets were removed surgically, leaving five pellets in situ. The pellets showed an average breakdown rate of 0.28 mg. per day.

Despite the removal of the pellets observation during the next four months showed no improvement in his clinical condition. The hypertension and angina persisted, and the blood electrolytes remained normal in the face of poor appetite and strength and slow loss of weight. On April 30 he was again admitted to the hospital because of increasingly frequent attacks of sweating, coldness of the extremities, dizziness, and faintness, usually associated with a feeling of hunger and relieved by fruit juice. A glucose tolerance test showed a low flat curve, at the conclusion of which he had typical hypoglycemic symptoms, promptly relieved by orange juice. An electroencephalogram taken while fasting showed diffuse delta activity, uninfluenced by the administration of glucose. Because of previous observations on the inefficacy of the synthetic desoxycorticosterone acetate on the disturbance in carbohydrate metabolism [12] he was started on Upjohn's adrenal cortical extract, which was administered in a dose of 1 c.c. twice a day for 16 days. At the end of this period there was a slight but definite improvement in the appearance of the glucose tolerance curve, which returned to its original state one week after discontinuing the cortin. However, spontaneous hypoglycemic attacks occurred much less frequently.

In June, 1940, approximately 11 months after the implantation of pellets, his precordial pain began to diminish somewhat, his blood pressure decreased to 110 mm. Hg systolic and 70 mm. diastolic, and for several days prior to admission on June 12 he had noted nausea and diarrhea. The blood sodium was 135 m.e./L. and chlorides 101 m.e./L. Since the patient showed obvious signs of exhaustion of his pellets, he was given an intravenous infusion of saline, following which he felt much better, and then was started on 8 grams of sodium chloride daily without the use of hormone. His blood pressure was maintained at 120–162 mm. Hg systolic and 70–100 mm. diastolic, and two weeks later his blood sodium was 140.2 m.e./L. and chlorides 106

m.e./L. On salt alone he again complained of precordial pain. Withdrawal of extra salt for 48 hours resulted in a prompt fall in blood pressure to 102 mm. Hg systolic and 70 mm. diastolic and definite symptoms of insufficiency. The blood sodium at this time was 130 m.e./L. and chlorides 105 m.e./L. Because of the extreme sensitiveness of this patient to hormone and salt it was deemed inadvisable to reimplant pellets.

Subsequent observations during the following 14 months, in which the dosages of salt by mouth and desoxycorticosterone acetate by injection were frequently varied, eventually demonstrated that he could be maintained in good condition, with normal blood electrolytes, weight, and hematocrit without the toxic manifestations of hypertension and angina by taking 6 grams of sodium chloride daily and 1 mg. of desoxycorticosterone acetate intramuscularly every three days.

In April, 1941, a trial of therapy with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was made. At the onset of treatment the patient's weight was 110 pounds, hematocrit 36 per cent, blood pressure 130 mm. Hg systolic and 80 mm. diastolic, blood sodium 143 m.e./L. and chlorides 107.5 m.e./L. Prior to this he had been receiving 1 mg. of the hormone intramuscularly and 4 gm. of salt daily. One week after receiving 1 mg. of the sublingual preparation in addition to 4 gm. of salt daily, his weight was 112 pounds, hematocrit 38.5 per cent, blood pressure 136 mm. Hg systolic and 80 mg. diastolic, blood sodium 137 m.e./L., and chlorides 101 m.e./L. On 4 gm. of salt without added hormone for a week there were no appreciable changes in these figures.

The results in this patient, who was implanted with pellets early in our experience, demonstrate the hazards of pellet implantation before adequate requirement stabilization has been achieved. Despite the removal of eight of the 13 implanted pellets the patient remained incapacitated by hypertension and angina pectoris. His appetite and strength were poor. He lost weight, probably because of a low caloric intake, and spent an inordinate amount of time in the hospital. Only after the remaining five pellets were exhausted did it become apparent that he could be well maintained on the small dose of 1 mg. intramuscularly every three days and 6 grams of salt a day. On salt alone he does not do as well as he does when receiving a small amount of hormone. This patient apparently falls into a small group whose requirement for hormone is so low and whose sensitivity is so great that pellet implantation is impractical. The dangers of hypoglycemia while receiving desoxycorticosterone and the response to cortin are again demonstrated here.

Case 4. L. C., a 35-year-old man, previously reported as case 4, had three pellets of desoxycorticosterone acetate, average weight 125 mg., implanted on January 6, 1940. He had been under treatment with the synthetic hormone for two months prior to this, and had been stabilized at a dose of 1.5 mg. of the hormone intramuscularly with 5 grams of salt daily. He was discharged taking 5 gm. of salt a day. His blood pressure was 110 mm. Hg systolic and 70 mm. diastolic, blood sodium 140.1 m.e./L., and chlorides 106 m.e./L. The hematocrit was 40 per cent, and he weighed 136 pounds (62 kg.) as compared with 129 pounds (59 kg.) on admission. During the first six months following implantation he did not show any further subjective improvement and did not feel strong enough to return to work or to lead a normally active life. His weight fluctuated between 136 and 142 pounds (62–64 kg.), his blood pressure was approximately 115 mm. Hg systolic and 80 mm. diastolic, and his blood electrolytes remained normal. His salt intake was increased to 9 grams a day. However, starting in the seventh month gradual and progressive subjective improve-

ment became apparent and was manifested by his indulging in normal activities including considerable exercise, such as wood-chopping. No objective changes occurred at this time. Ten months after implantation two pellets were still palpable and his condition was excellent. On December 26, 1940, almost one year after implantation, he was readmitted because of the recurrence of weakness, anorexia, and weight loss during the previous few weeks. On admission, his weight was 121 pounds (55 kg.), hematocrit 46 per cent, blood sodium 135.0 m.e./L., chlorides 100 m.e./L., and his blood pressure 104 mm. Hg systolic and 60 mm. diastolic. When the added daily salt was discontinued for four days his weight fell to 118 pounds (53.7 kg.), the hematocrit rose to 49.8 per cent, the blood pressure fell to 88 mm. Hg systolic and 58 mm. diastolic, the blood sodium and chlorides fell to 129.0 m.e./L. and 96.0 m.e./L. respectively, and the urea nitrogen rose to 22 mg. per cent. The patient felt very weak, and it was necessary to administer intravenous saline. After restabilizing the patient on the intramuscu'ar hormone for several days, he was implanted with three pellets on January 10, and discharged shortly thereafter in excellent condition, taking 5 grams of added salt a day. The blood sodium on discharge was 144.0 m.e./L. In the nine months since discharge he has led an entirely normal life, and has had no manifestations of either insufficiency or overdosage. His blood pressure averages about 110 mm. Hg systolic and 85 mm. diastolic.

Deliberately under-implanted the first time, this patient did not show a striking subjective response to therapy for at least six months. Eventually, however, his requirement apparently began to approximate the dose he was receiving, and he did very well. Exhaustion of the pellets was manifested by obvious signs of adrenal insufficiency.

Case 6. N. R., a 35-year-old married taxicab driver, was entirely well until July 1939. At that time he began to have vague generalized abdominal cramps associated with belching. A physician prescribed powders which relieved him. Following this, he had several episodes of abdominal pain which would come on three to four hours after meals and would be relieved by eating and by powders. Roentgen-rays of the gastrointestinal tract were negative for ulcer, and the gall-bladder series was normal. In May he noted that the skin of his upper extremities and face was becoming darker, but he attributed this to sunburn. He began to develop fatigability and some dyspnea on exertion. Two days before admission he had several bouts of vomiting. For some time his appetite had been poor.

The physical examination revealed a well developed and well nourished man with generalized brownish pigmentation most marked over the upper extremities and face. There were patches of dark pigmentation on the buccal mucosae. The heart and lungs showed no abnormalities. The blood pressure was 88 mm. Hg systolic and 60 mm. diastolic. No abnormalities were noted in the abdomen. The peripheral pulses were patent except for the posterior tibials. The deep reflexes were generally depressed but equal. There were no pathological reflexes.

The hemoglobin was 97 per cent, white blood cells 10,200 with 51 per cent segmented polymorphonuclears, 4 per cent non-segmented, 36 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophiles, and 1 per cent basophiles. The urine and stool were negative. The electrocardiogram was normal and roentgen-rays of the chest and abdomen showed no abnormalities. The blood Wassermann was negative. The hematocrit was 45 per cent, chlorides 490 mg. per cent, urea N 24 mg. per cent, sugar 85 mg. per cent. The glucose tolerance curve (after therapy) was 90, 95, 115, 90, 100 mg. per cent.

On admission the patient presented the classical signs and symptoms of untreated Addison's disease. He was started on an intravenous infusion of normal

saline for 24 hours, following which there was marked symptomatic improvement, and his blood pressure rose to 100 mm. Hg systolic and 68 mm. diastolic. For one week he received salt alone, taking 12 grams a day. Although the blood chlorides rose to 615 mg. per cent, there were no other appreciable changes. On July 29 daily treatment with 2.5 mg. of desoxycorticosterone acetate intramuscularly and 8 grams of salt was begun. After 10 days his hematocrit had fallen to 35 per cent and his weight had increased from 141.5 pounds (63.8 kg.) to 146.5 pounds (66.6 kg.), but his blood pressure remained low, 98 mm. Hg systolic and 70 mm. diastolic, and he still felt quite weak and anorexic. The dose of hormone was, therefore, increased to 5 mg. a day. After three weeks of this therapy his weight had increased to 150 pounds (68 kg.) and his blood pressure had increased to 110 mm. Hg systolic and 70 mm. diastolic. He was taught to administer the hormone himself and was discharged to be observed for several months prior to implantation of pellets.

Two weeks after discharge he was feeling very well. His blood pressure was 130 mm. Hg systolic and 90 mm. diastolic, his blood sodium 138 m.e./L., chlorides 104 m.e./L., and his weight was unchanged. Salt was reduced to 6 gm. a day. One week later his blood pressure was 142 mm. Hg systolic and 100 mm. diastolic, and the daily dose of hormone was reduced to 3 mg. a day. He was now able to return to his occupation of cab driver. On October 3 his blood pressure was 130 mm. Hg systolic and 90 mm. diastolic, and the hormone was cut to 2 mg. a day. A week later, the dose was reduced to 1.3 mg. and on October 21 to 1 mg. a day. At this time his weight was 152 pounds (69.2 kg.), his blood pressure 142 mm. Hg systolic and 90 mm. diastolic, blood sodium 144 m.e./L. and chlorides 109 m.e./L. On this dose for five days he lost three pounds in weight and his blood pressure fell to 105 mm. Hg systolic and 75 mm. diastolic. It was, therefore, felt that his requirement was more than 1 mg. daily, and on October 30, four pellets of desoxycorticosterone acetate, with an average weight of 127 mg., were implanted. This was intended to yield about 1.2 mg. of hormone per day. During the subsequent 10 months of observation he has done extremely well, indulging in full activity as a cab driver. His blood pressure is 130 mm. Hg systolic and 80 mm. diastolic and his weight 154 pounds (70 kg.). The blood electrolytes have remained normal and, as yet, he has shown no evidence of exhaustion of the pellets.

This case demonstrates the value of prolonged and careful observation of the response to the intramuscular preparation and the determination of the smallest possible dose which will maintain the patient, before implantation is performed. In previously untreated patients the hormonal requirement will very definitely decrease during the first few months of successful therapy. Failure to take this into account is responsible for the appearance of overdosage manifestations.

Case 7. J. K., a 46-year-old delicatessen clerk, who complained of fullness after eating and occasional nausea of three years' duration, was first admitted on August 16, 1940. Roentgen-ray studies eight months previously were said to show a duodenal ulcer. Five weeks before admission, he gradually lost his appetite, became weak, and had nausea after eating. He lost nine pounds and noted that his skin was becoming darker. For one week he had dyspnea on exertion and dizziness on arising from his bed in the morning. He has noted a definite craving for salty foods.

Physical examination revealed a thin, well developed man, with deep pigmentation of the skin and several bluish-brown pigmented areas on the buccal mucosa and hard palate. The heart and lungs were clear. The blood pressure was 80 mm. Hg systolic and 60 mm. diastolic while reclining, it fell to 70 mm. systolic and 60 mm. diastolic

after standing, and was associated with dizziness. The lower pole of the right kidney was palpable. The superficial reflexes were absent.

On admission on August 16, 1940, the patient weighed 131 pounds (59.5 kg.). His blood pressure was 86 mm. Hg systolic and 60 mm. diastolic, and the hematocrit was 41 per cent. The blood urea nitrogen was 24 mg. per cent, and a glucose tolerance curve showed a maximum use of the blood sugar to 120 mg. per cent. Unfortunately, because of technical difficulties, the blood electrolyte studies could not be done at this time. He was started on 12 grams of added salt a day and after two weeks of this régime he showed considerable symptomatic and objective improvement. His weight rose to 142 pounds (64.5 kg.), his blood pressure to 110 mm. Hg systolic and 70 mm. diastolic, and his hematocrit fell to 37 per cent. The postural hypotension disappeared. The blood sodium at this time was 133.5 m.e./L. and chlorides 102.0 m.e./L., urea nitrogen 9 mg. per cent. The added salt was now stopped for one week, at the end of which time he felt definitely weaker, although his blood pressure did not show any change. He lost two pounds in weight, and his hematocrit rose to 42 per cent. The blood sodium was 136.6 m.e./L. and chlorides 102 m.e./L. From September 11 to 17 he received 5 mg. of desoxycorticosterone acetate intramuscularly and 8 grams of salt daily. On this he gained 10 pounds in weight and his hematocrit fell to 34 per cent, whereas his blood pressure rose to 145 mm. Hg systolic and 90 mm. diastolic. Hormone and salt were then again stopped for 10 days, during which time there was a progressive loss of weight to 140 pounds (63.6 kg.), a fall in blood pressure to 110 mm. Hg systolic and 70 mm. diastolic, and a rise in hematocrit to 40 per cent, associated, however, with only a slight decrease in the feeling of well-being. Sodium chloride balance studies at this time demonstrated that on an intake of approximately 5 gm. of salt (ward diet) a day he was excreting 15.16 grams of NaCl. For 48 hours his salt intake was cut to less than 0.5 gram a day, and on this he excreted 7.75 grams and 4.06 grams of sodium chloride per day. This remarkable negative salt balance was reflected in the blood sodium and chloride values which were 127.3 m.e./L. and 96.0 m.e./L. respectively. His weight decreased and his hematocrit rose to 44.5 per cent during the 48 hour period. His blood pressure was sustained until the very end of the period, when, on getting out of bed, he suddenly felt very weak and faint and at that time his blood pressure was 88 mm. Hg systolic and 55 mm. diastolic. Intravenous saline, salt by mouth, and 5 mg. of synthetic hormone were administered and he made a prompt recovery. On three days of treatment with 5 mg. of hormone and 6–12 grams of salt a day, he gained 10 pounds (4.5 kg.), his hematocrit fell to 32.5 per cent, and his blood pressure rose to 140 mm. Hg systolic and 90 mm. diastolic. These studies having established the diagnosis of Addison's disease beyond any doubt, the period of stabilization and assay of hormone requirement was begun. He was discharged on October 13, taking 2 mg. of hormone administered by himself and 6 grams of salt daily.

One month later he was feeling very well, but his blood pressure had reached 150 mm. Hg systolic and 98 mm. diastolic. The hormone was, therefore, reduced to 1.5 mg. daily and a few days later to 1.0 mg., and the salt to 3 grams a day, since the blood pressure remained elevated. His weight was 150 pounds (68.2 kg.), and there was no edema or evidence of cardiac failure, although he did occasionally complain of palpitation. A palpable liver was noted for the first time, and it has remained palpable ever since. On December 3, almost two months after discharge, he was readmitted for pellet implantation. His weight was 151 pounds (69.7 kg.), his blood pressure 145 mm. Hg systolic and 85 mm. diastolic, and hematocrit 34 per cent. It was felt that his requirement was less than 1 mg. a day, and on December 8 two pellets with an average weight of 125 mg. were implanted and were calculated to yield approximately 0.6 mg. of hormone a day for about one year. Following implantation, his blood pressure showed a gradual downward trend to 110 mm. Hg systolic and 70

mm. diastolic to 135 mm. systolic and 80 mm. diastolic, and his hematocrit rose to as high as 42 per cent despite increasing the salt intake to 10 to 12 grams a day. Nevertheless, he felt extremely well and his weight increased to 159 pounds (72.3 kg.). However, in view of this apparently large requirement of salt which seemed necessary to keep him in good condition, it was decided to implant one more pellet and reduce the salt intake to 6 gm. a day. Accordingly, this was done on December 24.

Within two weeks of the implantation, the patient returned weighing 163 pounds (74.1 kg.), with edema of the face and legs, and with a blood pressure of 150 mm. Hg systolic and 90 mm. diastolic. His appetite and strength had decreased and he complained of headache. Added salt was discontinued and he was advised to avoid salty foods. Two weeks later there was no change. His blood sodium and chlorides at this time were 145.7 m.e./L. and 101 m.e./L. respectively. Potassium chloride in a dose of 3 grams a day was administered for two weeks without effect. He was, therefore, readmitted to the hospital for removal of a pellet. On admission, his weight was 160 pounds (72.8 kg.), blood pressure 140 mm. Hg systolic and 100 mm. diastolic, hematocrit 41 per cent, blood sodium 141.5 m.e./L. and chlorides 100 m.e./L. On March 3, one month after removal of the pellet, there was still no change in the edema. The patient's weight was 164 pounds (74.5 kg.), and his blood pressure 140 mm. Hg systolic and 90 mm. diastolic. Thereafter, however, there was a gradual spontaneous disappearance of the edema, loss of weight to 153 pounds (69.5 kg.), and fall in blood pressure to 130 mm. Hg systolic and 80 mm. diastolic. Strength, appetite, and general feeling of well-being improved sufficiently to enable him to return to his occupation as a delicatessen clerk. During the summer he took 2 grams of added salt a day. At present, 10½ months after implantation, he is beginning to show symptoms which may herald the exhaustion of his pellets.

This case demonstrates the marked sensitivity of some of these patients to relatively small variations in salt and hormone intake. A gain or loss of 10 pounds in weight and 10 per cent in the hematocrit in a short time was not unusual. It is interesting to note that, with the exception of the salt deprivation test, the blood electrolytes were never low enough to be diagnostic. The marked variations in weight, hematocrit, and blood pressure, and the disappearance of postural hypotension after salt administration alone were sufficient to establish the diagnosis. The caution which must be observed with the salt deprivation test is again demonstrated here. The occurrence of edema and hypertension after the addition of one pellet yielding approximately 0.3 mg. a day, its failure to subside after limitation of sodium chloride intake and administration of potassium, and its persistence for approximately a month after the removal of this pellet, are interesting.

Case 8. H. J., a 36-year-old German refugee with a family history of tuberculosis, was first admitted on December 10, 1940. For the past year she had been living with a relative who had open tuberculosis. She had always been dark-skinned, but had noted increasing pigmentation of the skin and mucous membranes during the past two years, and especially during the past few months. One and a half years previously she had had a low-grade fever, and eight months before admission developed fever and pain in the left chest. Seven weeks before admission she had had a low grade fever again and had noted generalized malaise and marked weakness. Occasionally during the past few weeks she had vomited.

Physical examination revealed a well developed female with marked pigmentation of the skin and mucous membranes. The tongue showed linear gray pigmentation in

rings near the circumference. There was marked grayish-brown pigmentation of the gums and lips and a few pigment patches on the buccal mucous membranes. The skin showed diffuse brown pigmentation, slightly darker on the face, and with a distinct exaggeration in the perineum, axillary folds, areolae of nipples and dorsum of the knuckles. The creases of the palms were brown, and there were several inky black freckles on the face and arms. The heart and lungs showed no abnormal physical signs. The blood pressure was 105 mm. Hg systolic and 80 mm. diastolic. The blood urea nitrogen was 16 mg. per cent, the serum sodium was 129.1 m.e./L., the chlorides were 96 m.e./L., and the potassium was 5.3 m.e./L. The glucose tolerance test revealed a flat curve with a maximum rise of the blood sugar to 105 mg. per cent.

On admission the patient was considered to be a typical case of Addison's disease in moderate adrenal insufficiency. For this reason she was started on a continuous intravenous infusion of normal saline. In addition, she received 12 grams of sodium chloride by mouth and 10 mg. of desoxycorticosterone acetate intramuscularly daily. At the onset of therapy the blood pressure was 92 mm. Hg systolic and 65 mm. diastolic. After receiving 2100 c.c. of saline intravenously, in addition to the salt by mouth, in the course of 48 hours, she improved considerably and the intravenous saline was discontinued. During the next few days the intake of salt was cut to 2 to 6 grams a day, depending on her clinical appearance from day to day. Desoxycorticosterone was reduced to 5 mg. per day. The blood pressure rose to 102 mm. Hg systolic and 64 mm. diastolic. The hematocrit was 31 per cent. At this time the patient began to show mental symptoms. She was alternately euphoric and depressed. She continued to take fluids by mouth and imbibed large quantities of fruit juices. Because of the psychotic state and the vomiting, 5 per cent glucose in saline was administered. On the possibility that the psychosis may be in some way related to disturbed carbohydrate metabolism in the central nervous system, and since the desoxycorticosterone acetate is known to have no appreciable effect on carbohydrate metabolism, the latter was discontinued and Upjohn cortical extract, in doses of 5 to 10 c.c. daily, was administered. At no time during this period was a low blood sugar found. It was eventually felt that the psychotic episode represented an exhaustive psychosis. After three days the mental state improved. Because of a slight rise in hematocrit and fall in blood pressure, the desoxycorticosterone was given again in dose of 5 mg. a day. After eight days the cortin was discontinued, and the dose of sodium chloride by mouth was set at 8 gm. per day. Three weeks after admission, her general clinical condition was good. Her weight was 128 pounds (58.1 kg.), blood pressure 114 mm. Hg systolic and 68 mm. diastolic, hematocrit 33 per cent, blood sodium 140.9 m.e./L., and chlorides 109 m.e./L. On January 18, five weeks after admission, the salt intake was reduced to 4 grams a day. At that time her blood pressure and weight were being maintained, although her hematocrit ranged between 34–38 per cent. Although her appetite and strength had improved, she complained of occasional chest pain and non-productive cough.

On January 27 a trial with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was begun. At the onset of this period her weight was 126 pounds (57.2 kg.), hematocrit 38.5 per cent, blood pressure 106–116 mm. Hg systolic and 60–80 mm. diastolic, blood sodium 150 m.e./L., and chlorides 114 m.e./L. Five mg. of the sublingual preparation were administered in a single dose each day for five days, and then 3 mg. for two days. During this period there was no change in weight. The hematocrit fluctuated between 36 and 40 per cent, and the blood pressure showed no change until the last day when it suddenly fell to 80 mm. Hg systolic and 60 mm. diastolic, coincident with the development of marked weakness and anorexia, necessitating the discontinuance of the studies. She also complained of further cough and some dyspnea. After receiving 5 mg. of desoxycorticosterone acetate intramuscularly, her blood sodium was 143.5 m.e./L. and chlorides 106 m.e./L.

On January 9, after being on 3 mg. of the synthetic hormone intramuscularly for five days, she suddenly developed fever, malaise, sore throat and increased cough. A throat culture demonstrated Beta hemolytic streptococci. The throat was red and granular with white follicles. The chest seemed clear. The white count was 12,000 with 80 per cent polymorphonuclear cells. The temperature rose to 105.2° F., and the blood pressure fell to 70 mm. Hg systolic and 40 mm. diastolic within a few hours of the onset of the acute illness. A continuous intravenous infusion of 5 per cent glucose in saline was started, and she was given 15 mg. of desoxycorticosterone acetate in divided doses and 5 c.c. of cortin. With this, the blood pressure rose to 105 mm. Hg systolic and 60 mm. diastolic and the hematocrit was 36 per cent. However, she continued to run a spiking fever to over 105° F. daily, became progressively less responsive, and her lungs became full of moist, bubbling râles. For this reason the salt intake was decreased by alternating the intravenous saline with glucose in distilled water. Fifteen mg. of desoxycorticosterone acetate and 5 to 10 c.c. of cortin daily intravenously were continued, but despite this the blood pressure fell to 60 mm. Hg systolic and 40 mm. diastolic, and despite sulfapyridine intravenously, the temperature remained elevated to over 105° F., and dullness and bronchial breathing appeared over the right lower lobe. The patient died on the fourth day of the acute illness.

Postmortem examination revealed extensive bilateral caseous tuberculosis of the adrenals; fibrocaseous tuberculosis of the left upper lobe with recent bronchogenic dissemination to the left upper and right upper lobes and hilar lymph nodes; calcified primary infection of the left upper lobe with calcified bronchial lymph node component; extensive focal and confluent bronchopneumonia of both lungs; marked edema of the lungs; fibrous obliteration of both pleural cavities; and diffuse brown pigmentation of the skin.

The patient's early response to therapy with the intramuscular desoxycorticosterone acetate was good. Preliminary observations with the sublingual preparation demonstrated that when administered in a single dose it was ineffective. Since it is probably incompletely absorbed and enters the blood at once, the inefficacy of a single dose is not surprising. The final fatal illness demonstrates again the low resistance these patients have, even when receiving presumably adequate replacement therapy, to infections which might, perhaps, not be serious in other individuals. The problems of therapy in this situation are apparent.

Case 9. S. K., a 57-year-old housewife, had been treated at another hospital seven years previously because of abdominal pain and vomiting which had occurred intermittently for at least two years prior to admission. Five years ago she had had an episode of what she termed "shock" consisting of marked weakness and semiconsciousness. Four weeks before the present admission she had begun to feel progressively weaker with constant faint feelings, headache, palpitation, nausea, and vomiting. There was no history of tuberculosis. There had been some anorexia and a weight loss of 25 pounds in five years.

The physical examination revealed a dark-complexioned middle-aged woman who appeared very weak, was uncoöperative, and resented examination. There were several small pigmented areas on the buccal mucous membranes. The lungs were clear, and the heart sounds were distant. The blood pressure could not be obtained by auscultation and was 60 mm. of mercury systolic by palpation. The reflexes were markedly diminished.

The urea nitrogen was 21 mg. per cent, sodium 123 m.e./L., and chlorides 94 m.e./L. A glucose tolerance curve revealed a fasting blood sugar of 90 mg. per cent;

half an hour later it was 160 mg. per cent; one hour 180 mg. per cent; two hours 95 mg. per cent; and three hours 100 mg. per cent.

The roentgen-ray examination of the chest was negative. Roentgen-rays of the abdomen revealed irregular calcific deposits above the superior poles of each kidney, representing calcified adrenal glands.

Treatment with 10 mg. of desoxycorticosterone acetate intramuscularly and 8 to 12 grams of extra sodium chloride by mouth daily was begun on March 13. Within six days the blood pressure had risen from 54 mm. Hg systolic and 36 mm. diastolic to 106 mm. systolic and 60 mm. diastolic; the hematocrit had fallen to 26 per cent, and the blood sodium was 133.0 m.e./L., chlorides 103 m.e./L. and the urea nitrogen 10 mg. per cent. With this there was marked subjective improvement. She now took an interest in her surroundings and her appetite improved. For the next three weeks, except for a period when she was on a salt deprivation test, she was maintained on 5 mg. of the synthetic hormone intramuscularly and 6 grams of salt daily by mouth. The blood pressure was maintained at about 100 mm. Hg systolic and 50 mm. diastolic; the blood electrolytes remained normal; and her weight was 120 pounds (54.5 kg.). The hematocrit rose slowly to 33 per cent, in which range it has subsequently remained. On March 25–26, a salt deprivation test was carried out. On a sodium chloride intake of 34 milli-equivalents (about 2 gm.) over a two day period she lost in her urine 186.9 milli-equivalents of sodium and 198.6 milli-equivalents of chloride, representing a considerable negative balance. Prior to the test, her blood sodium was 132 m.e./L. and chlorides 99 m.e./L. At the conclusion, the blood sodium was 135.9 m.e./L. and chlorides 99 m.e./L. At this time she complained of increased weakness, and her blood pressure fell to 90 mm. Hg systolic and 58 mm. diastolic.

After restabilization with 5 mg. of synthetic hormone daily, a trial period on the sublingual preparation of desoxycorticosterone acetate in propylene glycol was begun on April 8, four weeks after admission. After one week, in which she received 5 mg. in divided doses daily, her weight had fallen from 122 pounds to 118 pounds; her hematocrit had risen from 33 per cent to 37 per cent, although the blood pressure had increased to about 110 mm. Hg systolic and 70 mm. diastolic and the blood sodium was 133.4 m.e./L. and chloride 105 m.e./L. However, on the same dose of hormone and salt by mouth her weight spontaneously rose to 121 pounds and her hematocrit fell to 33 per cent in the course of another week. For this reason the sublingual dose of hormone was reduced to 2.5 mg. in divided doses for five days, again with no change in her status. All hormone was then discontinued, and she received only 6 gm. of added sodium chloride by mouth daily for nine days. Except for a slight fall in blood pressure to 92 mm. Hg systolic and 50 mm. diastolic there was no change in her status, her weight being 122 pounds, hematocrit 33 per cent, blood sodium 133.3 m.e./L. and chlorides 104 m.e./L. Although it was thereby demonstrated that she could be maintained on salt alone, it was felt advisable to use small doses of desoxycorticosterone acetate, so she received 1 mg. intramuscularly every other day. One week after starting this régime, her hematocrit had fallen to 29 per cent and her blood sodium was 130.5 m.e./L. and chlorides 94 m.e./L.

On May 21, about three weeks after having been restabilized, she suddenly developed fever, malaise, urticaria, herpes labialis and eosinophilia. The fever rapidly subsided, but the hormone was temporarily increased at this time. She was found to be sensitive to a number of plant inhalants and foods. After being taught to administer the medication herself she was discharged on June 3, taking 3 mg. every other day and 6 grams of salt a day. On June 18 her weight was 127 pounds, blood pressure 100 mm. Hg systolic and 60 mm. diastolic; blood sodium 142 m.e./L., and chlorides 108 m.e./L. One month later her weight was 128.5 pounds, her blood pressure 124 mm. Hg systolic and 76 mm. diastolic, and it was found she could be maintained adequately on only 1 mg. of the hormone twice a week. She was now having frequent episodes

of urticaria, and was found to be sensitive to the sesame oil which is the vehicle for the desoxycorticosterone acetate. For this reason some other form of therapy, such as pellet implantation, will be necessary in the future.

This woman, who undoubtedly had been suffering from adrenal insufficiency for some years and had finally reached a critical state before the true nature of her illness was established, showed a remarkable response to therapy. Because of the patient's age, the status of her cardiovascular system, and the prolonged hypotension, extreme caution was used in the administration of the hormone. That this was justified is apparent from the small dose necessary to maintain her after stabilization. No definite difference was noted between the response to the sublingual preparation plus salt and salt alone. However, it should be pointed out that, while the requirement for hormone is still changing, it is impossible to compare adequately different types of therapy. The occurrence of allergic reactions to the sesame oil has been reported before, and is an indication for either changing the oily vehicle for the hormone or the mode of administration.

Comment

Our experiences with the treatment of Addison's disease with desoxycorticosterone acetate during the past two and a half years have demonstrated that, provided proper precautions are taken, excellent results may be achieved. Not only are the abnormalities in electrolyte balance and blood pressure regulation completely alleviated, but there is usually a striking improvement in the strength and well-being of the patient, so that they can often return to their former occupations. It is now clear that failure to obtain improvement is usually attributable to either insufficient dosage or overdosage of hormone, or to the fact that the patient's symptoms are due predominantly to disturbances in carbohydrate metabolism.

In properly chosen and previously regulated patients the most satisfactory and economical method of treatment is by implantation of pellets. We feel that it is wiser, however, to implant less than the required number of pellets and to supplement treatment with some additional salt by mouth daily. In this way the dangers of unfortunate complications are lessened. By the sublingual route the hormone is definitely effective, but larger doses are needed than by the intramuscular route to produce equivalent results. Since by this method the hormone must be absorbed rapidly into the blood stream, it probably acts over a short period of time. For this reason it should be administered in small, frequent doses in order to produce an even effect. The ideal method of therapy is one in which there is a slow, steady release of hormone all day, a result which is best achieved by pellet implantation.

In order to obtain satisfactory results by pellet implantation, we feel that a prolonged period of observation while on treatment by the intramuscular route is necessary before implantation is carried out. During the first few months of treatment of a patient with the synthetic hormone, a gradual de-

crease in his requirement occurs. If pellets are implanted before the minimal requirement has been achieved, what was an adequate dose at the time of implantation will prove to be a toxic dose several months later. We now recommend that the patient be taught to administer the hormone himself and that he treat himself under home conditions for two to three months, using a small amount of added salt (5 to 6 grams). He should be seen at frequent intervals so that the dose of hormone can be promptly reduced on the appearance of hypertension, excessive gain in weight, or fall in hematocrit, these determinations being the most simple and reliable guides to therapy. When the smallest dose of hormone which will maintain the patient over a reasonable period of time has been determined pellets may be implanted. The number of pellets to implant is calculated on the basis that each pellet yields approximately 0.3 mg. a day, and the requirement by pellet is about 60 per cent of that required by the intramuscular route. Pellets of approximately 125 mg. in size should last about 11 months. In most cases exhaustion of the pellets is readily detectable by the gradual development of signs and symptoms of adrenal insufficiency. Reimplantation is simple, only a brief period of observation with the equivalent dose of hormone intramuscularly being necessary to demonstrate whether the requirement has changed. In those patients in whom a very small requirement of hormone is demonstrated, particularly if they are in the older age group, treatment with pellets is not advised because of the difficulty of controlling toxic reactions.

Toxic reactions, which were frequent early in our experience, were largely avoided later by extreme caution in the dose of hormone used. No fatal or life threatening reactions occurred. Hypertension, in one case accompanied by angina pectoris, was the most serious complication and occurred in four cases. The hypertension often did not appear until the patient had been receiving the hormone for some time, and often persisted for some time after the dose had been reduced. It did not seem to be correlated with the degree of salt and water retention. Elimination of the added salt or administration of potassium salts had little influence on the hypertension in our experience. In all cases the desoxycorticosterone had to be appreciably reduced and pellets removed if already implanted. Edema occurred at one time or another in four patients, and in only one was associated with any evidences of cardiac failure (case 2). Overdosage in some patients was characterized by weakness, malaise, headache, anorexia, salt distaste, and in one case (3) by eventual weight loss, probably due to decreased caloric intake. These symptoms are often difficult to differentiate from those of adrenal insufficiency. Three patients (cases 2, 6, 7) have developed palpable livers without evidence of cardiac failure or edema. The significance of this is not known. An allergic reaction in the form of urticaria was noted in one patient and this was demonstrated to be due to sesame oil, the vehicle for the desoxycorticosterone acetate. A different mode of therapy will, therefore, be necessary.

Seven of the eight patients have shown symptoms of hypoglycemia at some time while under treatment. In none have there been any appreciable changes in the glucose tolerance curve after therapy with desoxycorticosterone. In one case the symptoms were of sufficient severity to require the administration of cortin for their control. Another patient (not reported here, but who will be reported in detail by G. Engel and Margolin), whose adrenal disease was characterized preëminently by chronic hypoglycemia and neuropsychiatric manifestations, could not be managed at all with desoxycorticosterone acetate. In this type of case cortin may be preferable.

Two patients developed serious intercurrent infections, one terminating fatally. Two other patients successfully weathered severe upper respiratory infections. In the management of these complications we must again emphasize the importance of carefully regulating the doses of desoxycorticosterone acetate and saline lest the burden of cardiac failure be added. In the presence of severe crises, it may be necessary to use cortin intravenously in addition to other measures, since the oily solutions of the synthetic hormone can only be used intramuscularly.

Summary

1. Eight patients with Addison's disease were treated with intramuscular injections of desoxycorticosterone acetate in oil.

2. In six of these patients implantations of pellets of crystalline desoxycorticosterone were performed; two of these have had three implantations and one has had two. The value of this method of therapy is pointed out.

3. Use of desoxycorticosterone acetate in propylene glycol sublingually in four patients demonstrated that this preparation is not as effective as either the hormone in oil or pellets.

4. The technic of preparing patients for implantation of pellets and the importance of prolonged observation before implantation are emphasized.

5. The nature of the toxic reactions from desoxycorticosterone acetate and the methods of avoiding them are discussed.

6. The failure of desoxycorticosterone acetate to influence the disturbances in carbohydrate metabolism is again confirmed and the importance of hypoglycemic reactions emphasized.

7. Serious intercurrent infections occurred in two patients, one terminating fatally. The management of these complications is discussed.

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DEFORMITIES OF THE THORACIC SPINE AS A CAUSE OF ANGINOID PAIN *

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DURING the past 25 years considerable attention has been focused on the possibility of dorsal root pain simulating attacks of angina pectoris, and many suggestions concerning the differential diagnosis of both have been offered. From the time angina pectoris was recognized as a distinctive and important syndrome, many observers have cautioned against confusing it with similar complaints. In 1915 Allbutt [1] in his extensive monograph on arterial disease and angina pectoris, stressed the importance of distinguishing "true angina" from a host of other symptoms and from "nervous squalls." However, Sir James Mackenzie's [1] clear descriptions of cardiac pain widened the horizon, and led the way toward a more exact differentiation between angina and angina-like pain. In recent years more extensive observations in this field have been recorded. Gunther and Sampson [2] drew attention to the similarity between heart pain and the referred pain of root irritation in hypertrophic spondylitis. In an analysis of 50 cases they found that dorsal root pain may be projected around the chest or confined to one spot on the anterior chest wall; the pains might be paroxysmal in nature, and occasionally might be simultaneously noted in one or both arms. They felt they were able to draw well defined differences between real angina pectoris and dorsal root pain. Nachlas [3] noted that seizures of anterior thoracic pain might be due to osteoarthritis of the cervical spine, provoked by certain movements or quirks of the neck. He reasoned that irritation of nerves of the brachial plexus may produce such pain by referring it along motor nerves, particularly those innervating the pectoralis major and minor muscles. The importance of differentiating the pain of angina pectoris from the referred pain of spinal arthritis was again emphasized by Pardee [4] and by Fenn.[5] In addition, they pointed out that conditions such as diaphragmatic herniae, mediastinal tumor, herpes zoster and others may produce anginoid pain. Willius [6] stated that anginoid dorsal root pain may become pronounced when the patient with hypertrophic spondylitis is reclining, and a considerable degree of spinal relaxation is effected. Reid [7] found in a number of cases that cervical rib or a scalenus anticus syndrome induced root pain closely resembling angina. A case was recounted by Veil [8] of a woman suffering from cellulitis of the left breast, with concomitant substernal oppression which cleared up on eradication of the cellulitis. Others [10, 11, 12, 13] have drawn attention to the rôle of individual hyper- and hyposensitivity to pain, of the heart pains ac-

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companying fatigue and neurocirculatory asthenia, and of migraine, in the production of diagnostically confusing precordial distress. Most recently, Kellgren [14] has again reviewed the question and has cautioned against mistaking somatic pain, occurring about the chest, for angina pectoris.

Clinical Observations

During the past nine months we have observed 15 patients whose symptoms simulated angina, but were considered of dorsal root origin. To restate the clinical problem, four of these cases are reported in brief.

Case Reports

Case 1. McN., a 74-year-old farmer, entered Barnes Hospital in November, 1940 with the complaint of having had paroxysms of lower thoracic and upper abdominal pain for four years. He explained that the attacks were "really not pains, but feelings of discomfort or 'pressing' sensations." Attacks lasted from a minute to half an hour. On only one occasion was pain felt in the left shoulder and inner aspect of the left arm. The bouts were not related to meals, but were prone to occur at night especially when the patient felt chilly. Identical attacks were at times induced by such activities as shoveling, or exertions involving the upper extremities and trunk. Walking, running, or walking up a hill in a cold wind had never precipitated an attack. The patient's physician had considered this a case of angina pectoris and had treated it as such. Nitrites had been administered with indifferent results.

The past history was essentially negative except for the occurrence of a compression fracture of the twelfth thoracic vertebra 50 years before. This had healed at the time without complications.

Examination showed a tall, slender, well-preserved old man. There was a moderate senile emphysema. The heart was of normal size, with heart sounds distant but of "good quality." A blood pressure of 160 mm. Hg systolic and 85–80 mm. diastolic (lying) was recorded. The peripheral arteries were moderately thickened. There were no important abdominal findings. The spine was stiff and straight, showing a moderate lumbar kyphosis and flattening of the thoracic segment. Definite limitation of movement was noted in all parts of the vertebral column.

Routine laboratory tests were negative. Electrocardiographic studies showed no abnormalities. Roentgen-ray films of the entire vertebral column revealed a "moderate" osteoarthritis in all of the spinal segments; there was evidence of an old compression fracture of the twelfth dorsal vertebra. A chest film confirmed the clinical impression of cardiac size; in addition, moderate tortuosity of the aorta was shown.

The patient was seen by Dr. Frank Ewerhardt, under whose supervision a "cold water immersion test" (five minutes) was given. On the first occasion exposure to cold water reproduced a typical, transient attack of pain. Several days later the same treatment did not provoke an attack. An "articulator" was also applied to produce gentle traction on the spine. Stretching to a degree producing mild general discomfort induced an attack of paroxysmal lower thoracic pain, identical to those he had experienced spontaneously.

Case 2. C. G., a 58-year-old clergyman, entered Barnes Hospital in January, 1941 complaining of attacks of upper substernal pain. Two weeks before entry, while walking up a gentle slope to his home, he suffered the first attack of a painful sensation which he said felt like breathing cold air beneath the upper sternum. This did not

radiate. The pain was present for about one-half hour and disappeared on rest. Two days later, while sitting quietly, he had an attack of severe substernal pain which was noted also to occur along the inner aspect of both arms. Since that time there had been an attack every day. The bouts of pain usually appeared when the patient was sitting. Occasionally they occurred after meals. With the exception of the first seizure, exertion had not been noted to bring them on. The discomfort was usually a pressing sensation, not true pain, appreciated substernally and across the anterior surface of the upper chest. Ordinarily there was no radiation. The patient took nitroglycerin with each attack, but on no occasion did the drug relieve the pain.

Examination showed a large, rather obese man. The chest was barrel-shaped, the abdomen markedly protuberant. There was marked lordosis of the lumbar spine, and a definite, though not extreme, dorsal kyphosis. Motion of the spine was everywhere definitely limited. The apex beat of the heart was in the fifth intercostal space, 2 cm. outside the midclavicular line; the heart was considered slightly enlarged. The heart sounds were distant, but of "good quality." The blood pressure was 120 mm. Hg systolic and 75 mm. diastolic (lying).

Electrocardiographic studies showed evidence of myocardial change, in that the T-waves were altered in all leads. A chest film showed a thoracic cage that was very large, partly due to emphysema. The heart seemed to be slightly enlarged. A spinal film showed some lipping and spurring of the sixth, seventh, and eighth cervical vertebrae.

During the patient's stay in the hospital the severest attacks of substernal pain occurred while he was in bed, frequently at night. These attacks were not relieved by the administration of nitrites. Walking, stair climbing, and graded exercises did not precipitate pain. This patient was seen by the neurologist, Dr. S. I. Schwab, who believed that these were attacks of dorsal root pain due to hypertrophic spondylitis.

Case 3. M. G., a 45-year-old housewife, was seen in November, 1940, because of attacks of precordial distress and right costal margin pain which had occurred for the first time a month previously. Specifically, these attacks were characterized by sensations of oppression substernally and over the precordium with concomitant sharp knife-like pain extending from the back, along the left costal border. There was no radiation. The first episode occurred while the patient was at rest. A physician told her she was suffering a heart attack, and ordered her to remain at bed rest for a month. Subsequently the attacks of pain occurred several times each day, usually when the subject was doing her housework, but occasionally when she was lying down. In a few instances tingling sensations were felt in the left hand during an attack. The patient had been slightly short of breath on moderate exertion, but at no time was she orthopneic. Cyanosis and dependent edema had not been noted. Nitrites administered during the attacks gave indifferent results.

Physical examination showed a well-developed, well-nourished middle-aged woman. The interesting physical findings were limited to the spine which showed a definite moderate kyphosis, the greatest degree of flexion occurring in the sixth, seventh, and eighth dorsal segments, with limitation of all motion in the entire vertebral column. The heart was not enlarged. The sounds were of good quality. The blood pressure was recorded as 112 mm. Hg systolic and 70 mm. diastolic. The lungs were clear. There was an area of definite cutaneous hyperesthesia sharply localized about the cardiac apical region.

A number of electrocardiograms were taken during the time she was observed, all of which were within strictly normal limits. Fluoroscopy showed no enlargement of the heart; the lung fields were clear. Roentgen-ray films of the vertebral column (AP) gave no evidence of injury; small spurs in the mid-dorsal segments were attributed to hypertrophic change.

This patient was given a Taylor brace and an abdominal support, and was instructed to use a hard mattress when lying down for rest or sleep. The attacks of anterior chest pain almost immediately disappeared and have not recurred to date.

Case 4. M. H. was a 76-year-old, single, white woman, who had been a governess and practical nurse, and was first seen in November, 1940. She stated that for four years she had had paroxysms of pain, beginning at the precordium, and rapidly spreading to the shoulders, arms, and back. The precordial distress was likened to a feeling of heavy weight; concomitantly an indefinable sensation occurred in both shoulders radiating along the medial aspect of the arms to the elbows. Sharp, interscapular backache occurred simultaneously. As a rule such an episode of pain lasted for several minutes, but on several occasions had remained an hour or more. Between attacks there was precordial tenderness and mild pain in the shoulders on motion. These paroxysms usually came on at night while changing position in bed, though occasionally exertion such as climbing stairs precipitated them. A physician had considered this a case of angina pectoris and had advised the administration of nitroglycerin during an attack. When the drug was taken during the paroxysm slight relief was promptly gained; the attack was completely dispelled in 15 to 20 minutes, the patient insisted.

Examination showed a well nourished, aged woman. The upper thoracic spine exhibited a marked, though not extreme kyphosis, with definite limitation of motion. The head was carried forward and the lumbar spine showed the indenture of lordosis. The vertebral column thus assumed the shape of a well defined letter *S*. The ribs had been displaced upward and outward to form a barrel-chest. Heberden's nodes were prominent, and slight crepitus could be elicited in the shoulder joints on passive movement. On physical examination the heart was considered questionably enlarged. The heart sounds were distant but of good tone; a blowing systolic murmur was heard at the apex. The blood pressure was 150 mm. Hg systolic and 80–70 mm. diastolic (lying). The lungs were clear, and there were no objective evidences of cardiac failure. There were no definite cutaneous sensory defects.

Electrocardiograms showed diphasic T-waves in I, II and IV G, with depression of the S–T segment in I and IV, and "coving" in Lead III. It was interpreted as showing myocardial damage of coronary type. Spinal roentgen-ray films showed only very slight lipping and spurring about the vertebral margins, in addition to the gross changes in contour noted before. Other laboratory findings were negative.

Because of the character of the pain, its extreme irregularity of duration, and the circumstances usually precipitating it, the weight of evidence pointed toward dorsal root pain, despite the presence of probable coronary heart disease.

A specially made brace was applied to the shoulders and back in an effort to improve posture, and in addition her bed was equipped with hard mattress and fracture-boards. Following this no attacks occurred on exertion. For a month after the use of a hard bed was begun she continued to have paroxysms of pain at night. More recently these had diminished in severity, and for the past four weeks had been entirely absent.

The recognition of pain attributable to disease of the vertebral column is difficult, and in our limited series we have encountered the same doubts and obstacles as have been emphasized by many who have previously considered the problem. The symptoms of all of our cases resemble those of angina pectoris. Some features of the pain, its occurrence on exertion, its occasional short duration, and the partial relief often accomplished by the use of nitrites are suggestive of a cardiac origin. The majority of our patients described sharp pains in the back or elsewhere in the chest occurring simul-

taneously with precordial distress. Careful analysis of the symptoms usually revealed that the feeling of oppression beneath the sternum was superficial, and that the choking or strangling sensations so characteristic of true anginal attacks were absent.

Another possible differentiating point is the duration of the episodes of pain, which in some of our cases was greater than could reasonably be expected in true angina.

It seemed curious that many of these individuals obtained transient relief of symptoms on receiving nitrites. On the advice of their physicians, most of them carried nitroglycerin for use in the event of a seizure. The remission of symptoms resulting from this medication was not so complete as in angina pectoris, and frequently the pain gradually reintensified as the effect of the nitroglycerin diminished. There were occasions when the same patient experienced no relief from the drug. If indeed these patients were suffering from spinal nerve irritation, it appeared so doubtful that the discomfort could be relieved by such medication that we were inclined to believe the effect might have been psychogenic.

In order to investigate this question further, however, a number of patients, with painful osteoarthritis and rheumatoid arthritis and with myalgias, were given single doses of nitroglycerin without being told what to expect. When the apparent maximum effect was attained active and passive motions of the joints were performed and the myalgic patients were asked to move the painful muscles. More than half of these subjects stated that they experienced some relief during the height of nitrite action when painful joints were manipulated; in some this relief was fleeting, whereas in others the remission was definite, if transitory. It is difficult to assign a reason for this effect. Dixon [9] stated that he had noted relief of pain due to fibrositis by the use of nitrites. It is a common experience that heat, an active vasodilator, may confer temporary benefit on individuals with arthritis when locally applied. Rubifacients and other drugs promoting vasodilatation may accomplish the same. The simplest plausible explanation might appear to lie in the marked vasodilatation brought about by the nitrites. It would seem possible that by such influence the pain arising from mechanical pressure or by chronic inflammation might be temporarily allayed. The explanation is possibly less important than the realization that relief by nitrite medication may lead to diagnostic error.

Roentgenological studies of the vertebral column were not always helpful in establishing the diagnosis. In the cases reported only moderate osteoarthritis could be demonstrated. It seemed probable that the location rather than the extent of the bony change is determinant in causing irritation of the spinal nerves, and that pathological changes about the intervertebral foramina, not easily seen even in detail films, may be responsible for severe symptoms.

More significant than the roentgen-ray studies were postural defects which were evident in all of the patients of the group, and which were

attributable to disease of the vertebral column. In some there was straightening and stiffening of the dorsal spinal segment with limitation of motion; in others there was dorsal kyphosis of varying degree with markedly decreased movement of the spine.

In considering these cases it was realized, however, that such defects are extremely common, and that even when they are more evident and advanced, they are often asymptomatic.

The mechanism by which dorsal root stimulation is produced by hypertrophic spondylitis or other spinal deformity has not been satisfactorily explained. Usually ample attention has been paid to the character and distribution of the referred pain,[2, 3, 4, 15, 16] but the circumstances that may provoke it and the mechanics that operate to irritate the nerves have been but superficially considered or have not been mentioned at all. Nevertheless, a few reports have appeared from time to time which strike at the more basic aspect of the problem. Some years ago Sicard [17] spoke of funiculitis and radiculitis in the pains of lumbago and chronic postural errors. More recently Oppenheimer [18] has held that patients may develop segmental neuritis from crushing of nerve-roots caused by thinning of intervertebral discs and collapse of the intervertebral foramina. Morton [19] believed that diminution of the size of the intervertebral foramina was more common than thought. Others [20, 21, 22] have felt that osteophytosis frequently occurs about the transverse processes, spines and foramina which may irritate the roots on movement of the bones.

From the clinical standpoint most cases with anginoid pain show only moderate roentgenologically recognizable changes in the spine. Key [23] believes that in most instances of this type there is insufficient osteophytosis in the region of the nerve-roots to account for dorsal root irritation. However, in the clinical case the pain distribution over the chest and abdominal wall and the frequency with which movement of certain character produces it suggest that the irritation, from whatever cause, may be sharply localized in one or more spinal segments. As stated before, the physical sign that was constant in these cases was some postural deformity involving the vertebral column. That postural defects alone should in some way cause stimulation of the posterior roots at first seemed highly conjectural; however, on consideration of the anatomic relationships of vertebral column,[24] spinal radicles and the intercostal nerves, the question arose whether chronic deformities of the spine and thoracic cage might not exert traction on the nerves. Impingement of the nerve fibers in coursing through the intervertebral foramina, or tension at their connections with the spinal cord, might occur, with stimulation particularly of the sensory portion. It seemed possible that this might explain the curious neurologic picture in the presence of postural defects, where there was so little objective evidence of spinal disease. Therefore, an attempt was made to study the spinal nerves *in situ* in an effort to uncover more information as to the underlying cause of these clinical symptoms.

Experimental Observations

On a cadaver the large muscles of the back were removed in such a manner as to uncover completely the posterior thoracic wall and vertebral column. The posterior portions of the neural arches were removed, and the dura mater was incised longitudinally, the edges being held back by means of hooks. In this way the spinal cord and nerves from the sixth cervical to the

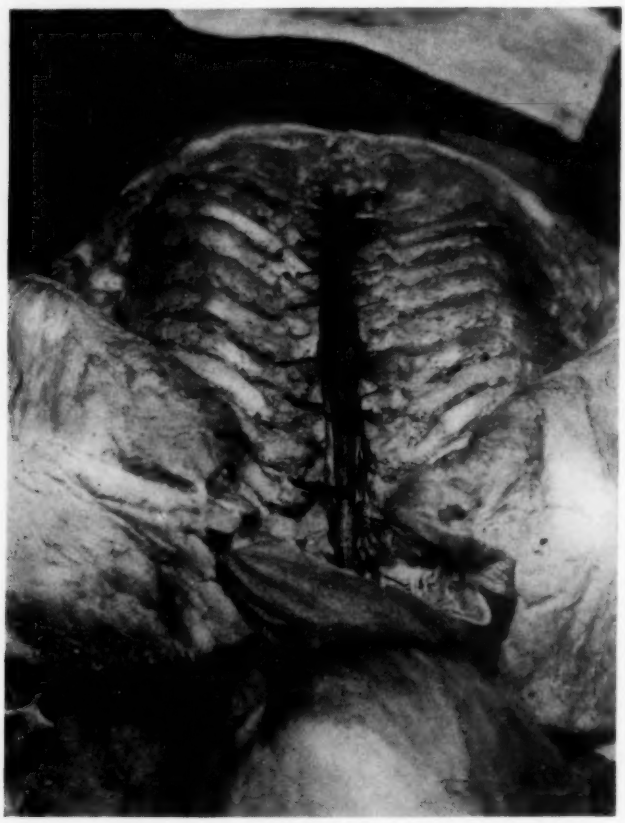

Fig. 1. The exposed spinal canal of the cadaver lying prone and with a normal curvature of the spine. Note the reference points (black lines) across cord, meninges and adjacent bones.

first lumbar vertebra were exposed. The contents of the thorax were next removed to gain access to the vertebral column anteriorly. In order to produce an artificial "kyphosis," wedge-shaped clefts were made in the anterior portions of the vertebral discs and bodies of the five upper dorsal segments. Care was taken to leave uninjured the articular structures between the vertebrae themselves; the clefts were sufficiently shallow so that no portion of the spinal canal was exposed anteriorly. This arrangement allowed the upper thoracic spine to be flexed abnormally to a position of extreme kyphosis.

It was found convenient to change the curvature of the spine by laying the cadaver prone; a rod was then passed under the thorax to the ends of which cords were attached and passed over pulleys in the ceiling and the opposite ends weighted. By this arrangement the thorax could be raised from the table, the upper thoracic spine falling downward in a marked "kyphosis." Horizontal traction to the head produced abnormal straightening of the spine.

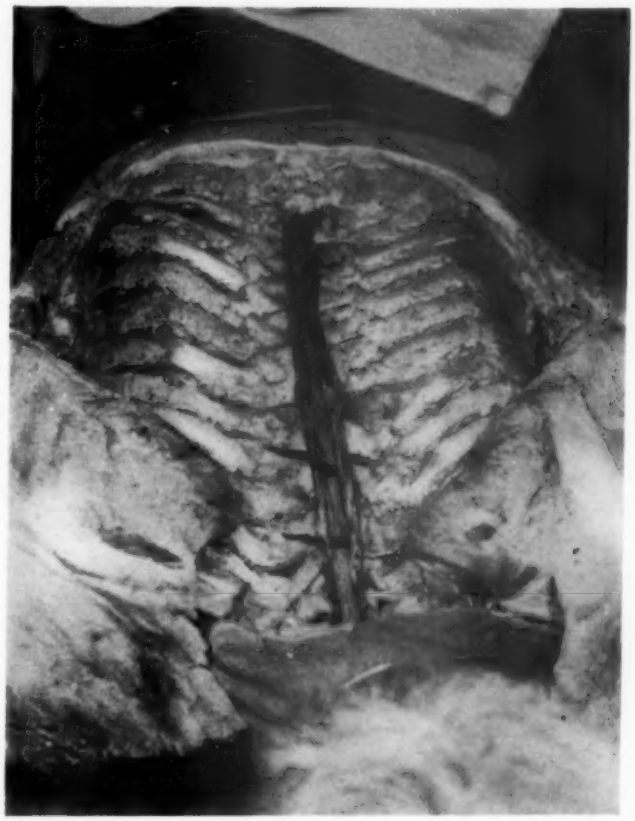

FIG. 2. Horizontal traction has been applied to the head of the cadaver to render the vertebral column abnormally straight. Note that the second reference point on the cord (caudad) has been displaced toward the head so that a stretch is applied to the spinal nerves (not shown).

The use of this dissection permitted direct study of changes of relationship and tensions applied to the spinal nerves during extreme flexion and extension of the vertebral column.

With the cadaver lying prone, without traction on the chest or neck, the curvature of the spine was essentially normal. The positions of the spinal nerves and the corresponding segments of the cord were noted in relation to the vertebrae and to the intervertebral foramina from which the nerves find exit. Horizontal traction was then applied to the head. As the spine

straightened, eliminating the normal dorsal curvature, the cord was placed under tension so that the reference points on the cord were displaced cephalad by 3 to 4 mm. Actually in straightening the spinal canal, there was an absolute displacement caudad of the vertebrae with reference to the cord. Such displacement would be expected to exert tension on the spinal nerve roots which would be particularly severe in two places: first at the

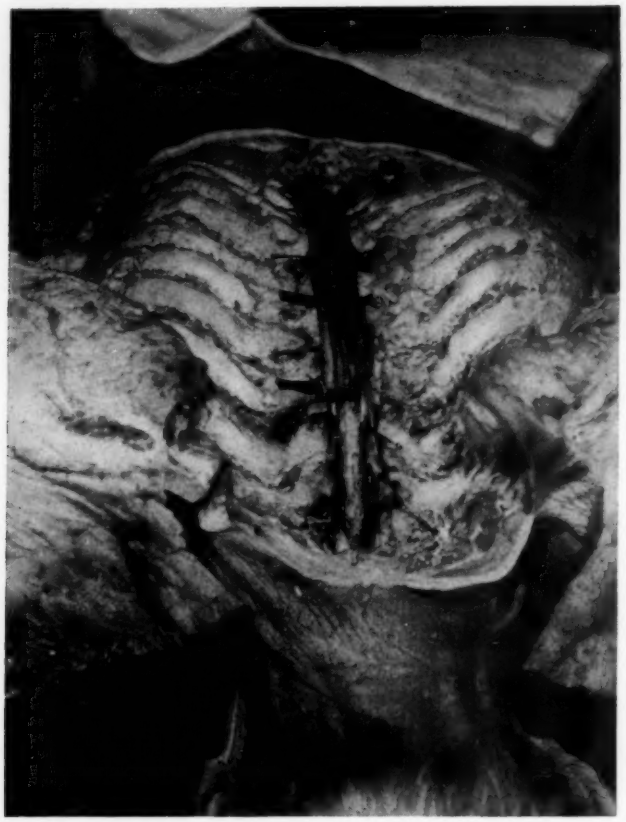

FIG. 3. The thorax of the cadaver has been lifted upward with collapse forward of the bodies of the upper dorsal vertebrae, producing a position of severe kyphosis. The reference lines on the spinal cord have been drawn markedly cephalad, placing extreme tension on the spinal nerves both at their attachments to the cord and at their angulation through the intervertebral foramina.

origins of the roots from the cord, and secondly at the portion of the root angulated in passage through the foramen. Palpation of the spinal nerves in this position showed them to be very much more taut than when in normal position. On release of traction to the head, the spinal column again resumed its normal curve so that the cord and nerves lay at their original vertebral levels.

Essentially the same degree of cord "displacement" was noted when artificial kyphosis was produced. It should be remembered that the articulations between the vertebrae were kept intact so that the kyphosis occurred by virtue of a closer approximation of the anterior surfaces of the bodies. When this was accomplished by raising the cadaver from the table the segments of the cord occupied a position relatively higher in the spinal canal. As in the former case, tension was thus applied to the spinal nerves because of their

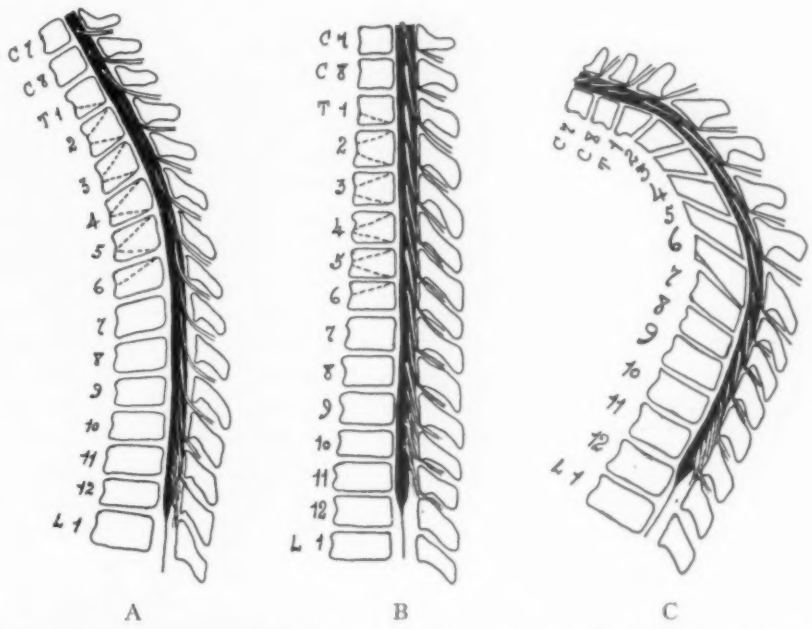

FIG. 4. Diagrammatic sketches, in exaggeration, of the spinal column and cord. A shows the normal vertebral column in relation to the cord and spinal nerves. The dotted lines in the vertebral bodies of T1-6 indicated the wedge-shaped clefts of bone chiseled away to permit abnormal flexion. B illustrates the position of the cord within the spinal canal on abnormal straightening of the spine. The cord is displaced cephalad. C shows the vertebrae in abnormal flexion (marked kyphosis). The spinal canal is thus lengthened (cf. text) and the cord again is drawn cephalad placing tension on the spinal nerves.

essential immobility at the intervertebral foramina, and this tension could be appreciated by palpation of the nerve filaments.

In the cadaver the displacement upward of the spinal cord when the vertebral column is either flexed or extended to an abnormal degree indicates that in either case the spinal canal is elongated. This becomes clear when one considers the mechanics. During hyperextension the vertebral bodies are separated and the articular facets between the vertebrae are separated as far as the ligaments will permit. In consequence of this, the cord is drawn cephalad. When the vertebral bodies are collapsed, and hyperflexion and "kyphosis" result, the spinal canal is again lengthened. The intervertebral discs function as cushions for the weight bearing bodies, and axes of the

intervertebral joints lie anterior to the bodies of the vertebrae. Therefore, hyperflexion (permitted by the wedge-shaped clefts) results in separation of the neural arches and subsequent elongation of the spinal canal. The relationship of the cord to the neural canal is thus changed as the cord is pulled cephalad, and tension on the spinal nerves is induced. The accompanying diagram shows, in exaggeration, these alterations in the level of the spinal cord.

Discussion

It is, of course, questionable whether tension on the spinal nerves at their fusion with the cord reaches such a degree under conditions of life, for one might expect that the dura mater, a tough membrane enveloping the cord and extending along the spinal nerves to the intervertebral foramina, would bear the stretch and spare the spinal nerves as deformity of the spine developed. However effectively the dura might function in this regard, the change of position of the meninges and cord with respect to the vertebrae could hardly eliminate the longitudinal tension imposed on the intradural spinal nerves. The gradual tension of the spinal nerves alone, growing out of progressive deformity of the vertebral column, could hardly be expected to produce the clinical symptoms. Schmorl [25] studied in great detail the changes occurring in the intervertebral discs which give rise to spinal deformities. He showed that swelling of the nuclear part of the discs may occur with evulsion, later, of the nucleus pulposus into the spongy portions of the vertebral bodies to produce atrophy and thinning of the contiguous bone. Nodular and calcific deposits may then occur in the cartilage and about the bony surfaces. The spinal deformities occurring in the wake of such cartilaginous and bony changes were thoroughly reviewed by Kountz and Alexander.[26] They showed that as swelling of the discs occurs the spine is abnormally straightened and stiffened. Progression of degenerative changes in the disc ultimately accomplishes thinning of the under- or overlying bone to such a degree that it can no longer support its burden, and collapse of the column at that point may occur. This results in kyphosis, which at first is slight, but later may become so extreme as to produce the common "hump." This process usually occurs in the upper dorsal portion of the vertebral column. In our cases it was during and after the time these alterations in spinal contour took place that clinical symptoms in the form of paroxysmal anterior thoracic and upper abdominal pain on motion apparently occurred. This also suggested the reason why, in so many instances, motion of a particular sort may precipitate the symptoms [3, 6] and why they may show such a multiplicity of types.[2, 15] An additional interesting suggestion is found in the work of Creuyx.[27] Creuyx believed that degenerative changes in the intercostal muscles could be demonstrated by studying their response to electrical stimuli, and that such degenerative change, occurring with spinal deformities and emphysema, resulted in fixity of the

thoracic cage in the position of inspiration. If this were true, then further immobility of the intercostal muscles and nerves might subject the nerve roots to irritation on motion of the vertebrae. However, Kountz and Alexander [26] and Clement [28] felt that costal rigidity was more likely a result of bony deformity than a disease of intercostal muscles and nerves.

It was emphasized earlier that measures which improved the posture of our patients alleviated or abolished their discomfort. In this connection the work of Kerr [29] is of some interest. He approached the treatment of angina pectoris from a unique standpoint with the supposition that angina may be the result of myocardial anoxemia enhanced by faulty refilling of the heart, and hence diminished oxygen supply to vulnerable tissues. Many of his patients had exhibited impairment of diaphragmatic motion which he thought might further reduce the return flow of blood to the heart. Kerr applied abdominal belts to these patients, and sought improvement in posture. Many of his subjects improved under this régime. In the light of our experience, it seems possible that the improvement he noted may have been due to the correction of general posture. Gallavardin [30] stated that some cases of angina pectoris have a "collaring sensation," as of a portmanteau placed about the shoulders, radiating about the shoulder-girdle. The attacks, he noted, were transient or of long duration, and might be provoked by movements of the upper extremities. He further stated that such episodes were usually indifferently relieved by nitrites. It is possible that Gallavardin may have been dealing with a problem similar to ours.

Summary and Conclusions

Report has been made of four of 15 patients having anginoid pain attributable to spinal deformity. Frequently the seizures could be induced by movements involving the deranged spinal segments. Procedures applied in an effort to improve posture brought about improvement or cure of the symptoms.

The mechanism of the production of dorsal root irritation was considered in the light of clinical findings, and an experimental study was made in order to investigate the problem further. This was done by using a cadaver, with spinal cord and nerves exposed, in which an abnormal degree of spinal flexion and extension could be produced. When the spine was either flexed or straightened to an abnormal degree, the spinal canal tended to become elongated so that the cord was drawn cephalad. This imposed tension on the spinal nerves particularly at their angulations through the spinal foramina and at their attachments to the cord. It was postulated that movement imposed on the nerves under such tension may give rise to irritation of the fibers with the production of referred pain.

Some of these patients experienced unexplained transient relief from the use of nitrites. It is emphasized that this phenomenon, if ignored, might lead to an incorrect diagnosis of angina pectoris.

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THE USE OF COLD IN MEDICINE *

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IN no period of medical history has so much progress been made in the conquest of disease as in the past few decades. One by one the infectious diseases have been pushed into the background; the deficiency diseases no longer pose major problems; even cancer, and the degenerative diseases of the cardiovascular renal system seem slowly to be losing out in their struggle for dominance over man. Scientific, specific bio- and chemotherapy have largely replaced the placebos, superstitions and nostrums of the past generation, yet the hot-water bottle and the ice-bag yield not one iota of their importance in our present-day therapeutic armamentarium.

It is my pleasant task to attempt to review the many uses which cold has found in medical practice. Just as in the case of heat, up until the past few years, hypothermy has been wholly a matter of local application to the superficial tissues, skin and mucous membranes. Only recently have attempts been made to reduce the entire body temperature as a therapeutic measure in various pathologic states, in a manner theoretically more or less analogous to the various forms of induced "fever" therapy so successfully employed in certain disorders. Obviously, it is too early entirely to evaluate the method, for it is frankly still in its experimental phases, and sufficient clinical data have not yet accumulated.

Before proceeding with the discussion of the therapeutic use of cold either locally or by the generalized reduction of body temperature to which have been applied various terms such as "refrigeration" and "hibernation" (Smith and Fay [59]), crymotherapy (Gerster and Sauer [29]), experimental hibernation (Vaughn [67]), hypothermia (Talbott [62]), and "frozen-sleep" (lay press), it might be well to review briefly some of the laboratory evidence upon which the use of reduced temperatures as a therapeutic agent is based. It should be stated at the outset that part of the evidence is contradictory and much further work will be necessary to clear up many of these discrepancies. Some of the difficulties may be technical, some of them may represent species differences, and some of them may be a matter of interpretation.

It is now some 10 years since Fay and Henny [24] first became interested in the problem of whether spinal cord lesions might produce localizing segmental dermatomere temperature changes of diagnostic significance through a hyperemia comparable to that which follows experimental stimulation of the reflex arc by heat or pain. As so often happens in such a study, the original quest became submerged by observations of far greater fundamental importance. In this case the problem evoked related to the effect of differ-

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ences in temperature upon embryonal, and by analogy, upon malignant cell growth. Geschickter and Copeland [30] had pointed out the well known fact that metastases from tumors were found chiefly in the warmer parts of the body. Primary tumors likewise were known to occur chiefly in the better vascularized, warmer areas, and to be rare below the elbows and knees as emphasized by Pack and his associates.[50] Huggins, Noonan and Blockson [36, 37] had recently demonstrated that the hematopoietic and reticuloendothelial tissues of the rat's tail and extremities could be maintained in the same state of activity as those of the central bones merely by preventing their temperatures from falling below 95° F. Coghill [15] had noted that the embryos of *Amblystoma punctatum* Cope, when subjected inadvertently to critical temperature levels during ice-box storage and subsequent incubation in every instance showed some maldevelopment. Smith and Fay [59] reported a similar finding in respect to chick embryos. If eggs were subjected to a critical temperature level of about 90° F. for the first 48 to 72 hours of incubation, and subsequently were incubated at 103° for the remainder of the normal 21-day incubation time, developmental defects of some degree would result with regularity.

On the strength of these various observations, some four years ago we advanced the theory, which was further supported to some extent by preliminary tissue culture studies, that there were differential metabolic requirements, or rather, different "critical" temperature levels for neoplastic as compared to adult differentiated cells.[59] This is a fundamentally different concept from that relating to the effects produced by the actual freezing of cells or tissues, with which our studies have frequently been confused. Many investigators have explored this latter field with somewhat conflicting results. Breedis and Furth [13] have conclusively shown that tumor cells could be preserved at —70° C. for periods of at least as long as a year provided, contrary to general opinion, that the freezing was permitted to take place slowly. Rahm [53] had the same experience with rotifers, nematodes and tardigrades, finding that with slow freezing they would survive temperatures of —253° C. Over 30 years ago Gaylord,[28] Michaelis,[44] and Moore and Walker [46] established the fact that Jensen's rat tumor would survive freezing in liquid air for as long as half an hour, and Ehrlich [22] at about the same time was able to keep cancer cells alive at —8° C. for as long as two years. On the other hand, Cramer [18] found no viable tumor cells in tissue cultures subjected three times to repeated freezing and thawing at temperature levels ranging from —20° C. to —40° C. Lambert [39] felt that cancer cells were more resistant to cold than were normal adult tissue cells. Auler [5] and his associates in exposing animal tumor tissues to 0° C. found that most of the transplants would subsequently grow. Bischoff, Long and Rupp [10] noted no permanent effect upon tumors in mice subjected to reduced body temperatures of as low as 19° C. (65° F.) for as long as 24 hours at a single time, or episodes of seven hours each, repeated four or five times.

Lucké,[41] in working with frog tumors, both in the natural host and as transplanted into the anterior chamber of the eye, came to the conclusion that temperatures as low as 4° C. were effective chiefly in influencing the rate of growth of the tumor, with subsidiary effects upon the form the growth took. These experiments were carried out with great care at 28° C., 7° C., and in one series of frogs subjected to hibernation, at 4° C. for 10 weeks. They seem to confirm the hypothesis of the importance of an optimal temperature for successful tumor growth. They are open to the criticism that the frog tumor is one generally accepted as viral in nature, and it is well established that viruses are preserved, not destroyed by low temperatures. The experiments are likewise not entirely analogous in that they are dealing with cold-blooded, poikilothermic animals rather than homeothermic warm-blooded mammals. In general, they tend to confirm our observations as to the universality of such physical laws as relate to the thermodynamics of biology. Perhaps the most complete reviews concerning the resistance of cells to extremes of cold are the recent ones of Belehradek,[7] Heilbrunn,[33] and Luyet and Gehenio.[42]

Fuller, Brown and Mills [27] came to the conclusion that the incidence and rate of growth of tumors in mice was heightened by keeping the animals in a reduced environmental temperature. They further cite the influence of climate on the incidence of cancer in man as shown by the preponderance of cases in the northern as compared with the southern states in this country. They make one interesting and important comment, stating that, in their opinion, the chief factor involved relates to the lack of body surface radiation in the colder environment. They make no comment regarding the actual body temperature of the animals in their experiments. All of this harks back to one of our own earliest comments that there is an optimal level for the growth of all cells, speaking in terms of physical wave lengths, both in respect to light and temperature.

Statistics on the world distribution of cancer are far from satisfactory. Although lower morbidity and mortality figures seem to prevail in the tropics, we must attempt to correct for the age factor, with its low average age at death as compared to that of the United States as a whole of nearly 65 years. Do the increased metabolism of the warmer climate, the earlier adolescence, the earlier climacteric physiologically balance the added years of life in the temperate zones, so that the cancer incidence actually can be compared?

In view of one of the chief clinical problems encountered both by ourselves and others in the use of general hypothermy, that of a somewhat atypical form of circulatory failure which occasionally occurs, we have been particularly interested the past few months in studying the effects of hypothermy on tissue cultures of heart muscle with the object in view of finding methods of compensating apparent cardiac failure. We have found but little previous work on striated muscle cell cultures of any kind which seemed particularly pertinent to our problem. Moran [47] felt that —2° C. repre-

sented a critical temperature level for normal frog muscle. Lake [38] found that — 7° C. was fatal for in vitro cultures of fetal rabbit heart. Hetherington and Craig [35] found the time factor was equal in importance to the reduced temperature in embryonic chick heart before explanting tissue.

In similar but rather more extensive studies [55c] upon fetal heart cultures, we have been impressed by several findings which occurred with great regularity. In the first place, if fetal heart muscle is stored at varying reduced temperature levels from 37° C. to 0° C. for 24 hours before explanting into culture medium, there is a latent period before such fragments of heart muscle start growing and beating which may be expressed as an almost straight curve, proportional to the temperature. In the second place, if the time interval at which such heart muscle is stored is prolonged the survival period increases as the temperature approaches zero in spite of the fact that the latent period is prolonged. In the third place, as Hetherington and Craig [35] noted, the volume or mass of tissue influences the survival rate, the larger fragments showing greater resistance.

Of more interest, perhaps, are those observations relating directly to the influence of lowering the temperature upon the actual implanted fetal heart muscle tissue cultures. At 37° C. the average survival period of normal active cell contractility and growth was about three weeks. At 27° C. activity could be maintained regularly for periods of six weeks or more with no evidence of diminished functional capacity. Cultures submitted to a "critical" 22° to 24° C. temperature level for periods up to four days would survive and convalesce but with progressively longer latent periods of up to 80 or more hours before functional activity was restored. Although the cultures themselves might, and usually did, survive a five-day period of "hibernation" at these levels, the cells individually as a mass showed no evidence of contractility during this time, nor did they recuperate functionally after restoration to the normal 37° C. body temperature level.

Physiological observations, many of which it has been possible to record cinematographically, show that with lowering of the temperature of the culture, there is a marked prolongation of the interval between contractions (latent time). The contractile phase is much less strikingly affected until the lower temperature ranges are reached, or until there has been prolonged exposure at critical levels. Finally, it is of interest to note that fibrillation can be induced at will, by the rapid lowering of the temperature to near 0° C.

Tuttle's [66] recent observations of the effects of decreased temperature on the activity of intact skeletal muscle as studied physiologically in human beings bears out these tissue culture findings. He noted the same prolongation of the relaxation time and explains on physiological grounds, for the first time to my knowledge, the rationale of, and the necessity for, the familiar "warming-up" of athletes before, as he puts it, "explosive bouts of exercise."

Sano and Smith [55] noted that a "critical" level around 22° to 24° C. existed in respect to the nuclear division of tumor cells in tissue culture, and

that only rarely would any tumor cells survive a period exceeding five days at a level of 20° C. By contrast,[55b] they found that a temperature of 25° C. was the optimal level in certain respects for the growth of fibroblasts in tissue culture. This they suggest may be of practical importance in wound healing, for the cells grow more compactly, with less collagen formation and, therefore, with less disfiguring and often, less painful scar tissue formation.

These general observations regarding the effects of reduced temperature upon cell growth and viability, although largely empiric and lacking almost entirely in respect to the finer details of cell respiration and metabolism, nevertheless seemed adequate to utilize as a basis for certain clinical observations.

Local Hypothermy

In the field of local hypothermy there has accumulated a vast experience and literature. As we have pointed out previously, Bennett [8] in 1849, Arnott [4] in 1851, Velpeau [68] in 1856 and Cooke [17] in 1865, all commented favorably upon the use of brine mixtures in the treatment of accessible cancers such as those of the cervix and breast. It is of more than passing interest that they used hypothermy not only to destroy the growth locally, but also for its anesthetic effect. Again, in 1872 S. Wier Mitchell [45] commented on his experiences in the Civil War regarding the value of cold therapy in the treatment of the pain associated with nerve injuries. Lortat-Jacob and Solente [40] in 1930, in an extensive monograph, review their own experience as well as that of some 300 other authors with "cryotherapie," the emphasis being placed almost entirely upon carbon dioxide as the cold agent. Its value in the treatment of birthmarks, various nevi, basal cell carcinomata, certain carefully selected squamous carcinomata, as well as many of the inflammatory dermatitides and degenerative dermatoses, is particularly stressed.

Our own work in the cancer field, using cold applied locally at 4° C. to 5° C. (38° to 40° F.), was begun in 1936 and has been carried on more or less continuously in a series of hopeless, inoperable terminal cases since that time. The clinical care of the cases has been under the direct supervision of Dr. Temple Fay and his associates. A committee made up of members of the various clinical and laboratory services has served in an advisory capacity in selecting cases, determining the type and extent of treatment, and in evaluating the results. A wide variety of types of tumor have been studied and reported both clinically [23, 59] and pathologically.[55a] They have included oral, esophageal, gastric, rectal, vesical, cervical and mammary cancer as well as brain tumors, bone sarcoma, lymphosarcoma, Hodgkin's disease and melanosarcoma. Regressive changes of variable degree have occurred regularly, even to the point of histological clearance of the local tumor bed in some few instances, as demonstrated by biopsy specimens taken at intervals during and following treatment.

In addition to the regressive changes noted in the tumors themselves, pain relief has been one of the most striking clinical results. This pain relief has not only occurred during the period of application of the cold, but in many cases has persisted for several days or even weeks following the removal of the cold as reported by Fay and McCravey.[25] Not infrequently it has permitted the reduction or complete withdrawal of sedation. Thus, as Arnott [4] so aptly put it nearly a century ago "even were the benefit . . . (of local hypothermy) to be limited to this (relief of pain) alone, there are few "recent" medical discoveries . . . which would exceed it in importance."

We have sought a physiological explanation of this phenomenon. In part the answer undoubtedly is supplied by actually cutting down the blood supply because of the vasoconstriction which accompanies the application of cold, thus reducing the familiar "stretch" mechanism upon the pain fibers. In part the answer may be expressed as a change in nerve conductivity through physico-chemical alteration of the lipoids by congelation. And, finally, the fact that cold acts as a true protoplasmic anesthetic, as recently suggested by Allen,[2] rounds out the concept.

As may be seen from these comments, the possibilities of local hypothermy in this one field of malignant disease alone require further extensive exploration and correlated study by laboratory and clinic alike. To us the evidence is convincing that local refrigeration has a very definite place in the therapeutic armamentarium of cancer. In our present state of knowledge, surgery is still the backbone of caner treatment. Supplementing surgery, and in certain specific types of cancer, even replacing surgery as the method of therapeutic choice, is irradiation. But irradiation is by no means the panacea we had hoped it might prove to be, and as an adjunct to both surgery and irradiation, hypothermy has much to offer, especially in the management of the terminal stages of the disease, altogether aside from any possible curative value it may possess. In the control of pain, in reducing narcotic requirements, in its bacteriostatic effect and resultant deodorant action, it makes life very much more bearable for the patient as well as simplifying the nursing problem. Through the almost invariable gross shrinking of the tumor mass often within 24 to 48 hours as a result of the vasoconstriction which occurs, with the consequent reduction in edema, not only of the tumor but also of the surrounding tissues, it may well provide a better opportunity for maximal irradiation effect in certain instances in which radium implantation is to be employed, as in cancer of the uterus. As is well known by the physicists, and constantly emphasized in our tumor clinic by our radiologist, Dr. W. E. Chamberlain,* the effective dosage of radium diminishes roughly as the square root of the distance from the point of application. Thus, reducing the volume of the tumor by preliminary hypothermia should tend to improve the chances of reaching the more distant cells with an adequate irradiation dosage. Furthermore, there is a rather widely held view that

* Personal communication.

tumor cells are more readily damaged during the period of mitosis. It has been shown by Sano and Smith [55] that a rather large proportion of tumor cells grown at the "critical" level of 22° C. to 24° C. tend to show "arrested," incomplete mitosis. Combining irradiation therapy with such hypothermia might well increase the effectiveness of both procedures, arguing on purely theoretical grounds. Thus far very few pertinent observations in respect to such possibilities have emanated from the laboratory. Breedis and Furth [12] have shown incidentally, in an experiment designed to prove that there was no virus element present in their tumor cultures preserved at —70° C., that radiation in well established effective dosage at normal temperature levels was equally effective at this subnormal level. On the other hand, Cook [16] demonstrated that Ascaris eggs exposed to a dosage of 5000 roentgens and then preserved at 5° C. for eight weeks developed 45 per cent normal embryos, whereas those eggs which were permitted to develop immediately at 25° following irradiation produced only 1 to 2 per cent normal embryos. They conclude accordingly that low temperature has a definite and beneficial effect upon the recovery from irradiation effects. Obviously the experimental factors are not strictly analogous, as the radiation was given first in this case.

Thus far my comments on the use of local hypothermy have related almost entirely to the field of malignant disease. You will perhaps excuse me for this in the realization that our primary interest and efforts have been pointed in this direction, with the hope that others would see its further possibilities and explore those fields in which their particular interests lay.

In connection with various pain problems Fay [23] has found local as well as general hypothermy of definite clinical value. In intractable types of headache, application of a cooling hood has almost regularly given prompt relief. Here we see the modern, streamlined version of the ice-bag, with accurately controlled temperature regulation. Similarly, the use of a cooling pad over the lower thoracic and lumbar regions is effective to a surprising degree in controlling lower abdominal and pelvic pain, apparently through reduced conductivity of pain impulses by the refrigeration effect upon the posterior roots, thus breaking the continuity of the reflex arc. Undoubtedly, the time honored use of the ice-bag on the abdominal wall over the appendix region depends upon a similar reflex action. It seems unlikely that the penetrating effect of cold applied locally to a thick abdominal wall could actually cause regression of the inflammatory process in the appendix by a true refrigeration effect, yet Selden [56] found a drop in temperature of as much as 7.5° F. to 15.6° F. in the subjacent intraperitoneal areas after 30 minutes of such application. Bierman and Friedlander,[9] in discussing the penetrative effect of cold, found that in the human being cold applied as ice bags to the calf of the leg for periods ranging from one and a half to two hours caused a temperature drop of the muscle two inches beneath the surface, of as much as 15° to 26.4° as recorded by thermocouple. The temperature of the male urethra was lowered as much as 23.8° F. in an hour and a half by applying

cold through a metal applicator in the rectum. Similar drops of temperature were observed in the rectum when water at 44° F. was circulated through such an applicator introduced into the vagina. In our own studies these observations have been confirmed time and time again, so far as the immediately adjacent tissues are concerned, but the refrigeration effect drops off very rapidly as the distance from the cold increases.

For the successful administration of local hypothermy metal applicators, preferably of silver or copper, are indicated as the best heat conductors. The applicators should fit the area accurately, for even a thin layer of air serves as an effective insulator, thus reducing the effectiveness of the treatment. They should be held in position firmly but without pressure, as pressure plus cold spells necrosis. The most satisfactory apparatus needs to be designed almost individually for the particular case. Blankets, hoods, boots, jackets, head-bands, and the like, of rubber tubing sewn between two thin layers of cloth, and thus serving as a closed circulatory system, give one more general flexibility in treatment. However, the insulating effect of the rubber, cloth and air must be taken into consideration and the circulating fluid must be considerably lower than that needed with the metal applicators. These various appliances can be attached to a special electrical refrigerator bedside unit * which circulates either water or a refrigerating solution such as Freone at a rate which assures a constant temperature at all times. The unit is applicable to the induction of either local or general hypothermy.

The most immediately practical use to which local hypothermy has been applied in other fields than cancer during the last few years has been presented by Allen and his co-workers in a series of papers [2] relating to the effect of variation in temperature upon circulatory disorders in general, and upon peripheral vascular disease in particular. In their most recently published paper [3] they report 45 cases of vascular gangrene on whom 57 amputative operations were performed. In the series there was only one death attributed to operative mortality, and six other deaths occurring within a six-week postoperative period which were dependent upon fatal conditions antedating the operation. More than half the patients were diabetic; 13 were women; seven were negroes; the ages ranged from 49 to 85 years, two-thirds of them being over 65 years. The advantages of the procedure are the absence of pre- or postoperative pain, the prevention of immediate postoperative shock and the lack of postoperative complications, particularly infection, thrombosis and embolism. In addition the patients retain their appetites and spirits. These cases, climaxing years of work in a search for a method of controlling and treating diabetic gangrene promise to become a milestone in the history of traumatic surgery of the extremities. McElvenny [43] has reported a case in which the method was used to control infection in a bilateral traumatic amputation, and it is certain that many such reports will be forthcoming in the next few months. Blalock and Mason [11]

* This apparatus may be obtained from the Therm-O-Rite Corporation of Buffalo, N. Y., who have coöperated in the development of satisfactory therapeutic equipment.

somewhat grudgingly confirm the physiological accuracy of Allen's studies in respect to the relationship of temperature reduction to a lowered incidence of shock.

Aside from the surgical aspects of Allen's work, there are several other possible clinical applications of the use of hypothermy in the medical treatment of peripheral vascular disease. It is Allen's contention that with ischemia of an extremity due to occlusive vascular disease the metabolic requirements of the tissues are not met by the diminished blood flow. Therefore, the use of heat is definitely contraindicated, as increased temperature increases cellular metabolic demands and the ischemic blood supply becomes still further inadequate. By reducing the temperature of the extremity, cellular metabolism is reduced, the blood supply is adequate and gangrene is prevented. Theoretically, at least, if this is maintained over a long enough period, repair and revascularization might take place. Freeman,[26] in a recent communication, confirms these observations and recommends that the temperature of the air around an ischemic extremity be maintained at 30° to 34° C. Brooks and Duncan,[14] using a very accurate and elaborate technical method, showed that rats' tails would survive complete ischemia for a period of more than 96 hours at 1° C. without the development of gangrene. Allen had previously shown[2b] that "when the temperature can be maintained at about 2° C. the limbs can survive asphyxia for a long period, the maximum of which has not been accurately established, but which is certainly more than 50 hours." From these observations it would seem that hypothermy is beginning to gain the recognition as a local therapeutic agent which it justly deserves.

General Hypothermy

As a result of the regressive changes which Smith and Fay[59] observed in cancerous growths from the local application of cold, and the striking interference with normal cell growth and differentiation noted in preliminary laboratory studies with reduced temperatures, it was but a logical step to attempt to reproduce a comparable lowering of the whole body temperature in order to find out whether similar regression might occur in deep seated metastatic lesions. Hydrotherapy and antipyretic drugs have been used clinically throughout the centuries for reducing the body temperature in fever, but only to restore the tissues to normal physiological levels. Considerable literature has accumulated on the effects of lowering the temperature of experimental animals. Recently Woodruff[70] has reported that dogs would not survive blood temperature of 80° F. for many hours. Simpson and Herring[58] and Troedsson,[65] however, have shown that in the cat, rabbit and even monkey (non-hibernating animals), a condition simulating hibernation can be induced by narcosis and a body temperature of 56° to 60° F. attained and maintained for hours.

The question of nomenclature regarding the physiological state of these patients has been the occasion of considerable controversy. For want of a better term we originally suggested "hibernation" (always in quotes) as being useful descriptively. It still is. In dealing with the patient of today it seems preferable to speak a language which he understands. He is not familiar with the fundamental physiological differences of temperature control of the homeotherms and the poikilotherms. He speaks of "fever" treatment with almost colloquial familiarity—not of hyperthermia. Cold narcosis would mean nothing to him, and the same might be said of cryotherapy, crymotherapy and hypothermia.

Obviously, "hibernation" is a misnomer scientifically. We might point out that a somewhat similar state develops in certain poikilothermic animals and reptiles during the dry, summer months, which is termed "aestivation." Thus, it is not a question of external temperature alone, but apparently a protective mechanism designed to preserve the life of the animal through periods of inadequate food or water supply. As a preliminary to this change the animal usually builds up a supply of fat or, in the case of the cold-blood animal, of water. Hunger or thirst, as the case may be, coupled with temperature changes seem to be essential to the development of the hibernating stage. Chamberlain,* for example, has remarked that he could induce hibernation in squirrels at any time of the year by starving them first for 24 to 48 hours and then putting them into a refrigerator. Without the initial hunger phase, however, he could not accomplish his objective.

The mechanism of hibernation is a complex one which has intrigued physiologists for centuries and which recently, perhaps in part stimulated by our studies, has been the subject of considerable investigation. Parker [51] has shown that certain tissues in fish can absorb hormones, and suggests the possible analogy that the lipoid tissues of the mammal may act in a similar way to inactivate normal metabolic activity. Sevringhaus [56a] has suggested a similar possibility in respect to the storage of estrogenic substances by fat, as explaining the less spectacular results obtained in obese patients undergoing endocrine therapy. It is, of course, well known that the ordinary hibernating animals such as the hedgehog have certain special fatty organs, sometimes spoken of as hibernating glands, which store huge quantities of fat. This is also true of the bear, and a rather close analogy exists in the "hump" of the dromedary to the nutritional needs and the maintenance of water balance of the animal, although hibernation in the usual sense of the word does not occur. Similarly the steatopygy of the Hottentot may well have a similar functional purpose, as Wells [69] has pointed out.

Akiyama [1] found that squirrels in hibernation were protected from what would otherwise be a fatal inoculation of a tumor producing virus. Tainter,[61] at Stanford, noted that animals failed to exhibit the usual toxic reactions to drugs like dinitrophenol if they were maintained at temperatures of 33° to 42° F. Suomalamen,[60] in Helsinki, found that the injection of

* Personal communication.

magnesium chloride would hasten the normal hibernation of animals in the fall, and that conversely calcium chloride prevented the development of the hibernating stage or brought the animals rapidly out of hibernation. He likewise noted low blood sugar and low adrenalin content of the blood in his animals. Pfeiffer,[52] in Chicago, working with the ground squirrel confirmed the work of both Suomalamen and Tainter. Even Harvey Cushing [19] some years ago suggested the probable importance of the pituitary in hibernation, because of its fairly well accepted relationship in water metabolism, and because he noted definite changes in the cells of such animals during hibernation.

Herrmann [34] and Barbour [6] in particular have stressed the physiological differences of thalamic temperature regulation in true hibernating animals and in the state which is induced by light narcosis and the reduction of body temperature in homeothermic mammals. They review certain of the theories regarding the nature of hibernation which have been propounded in the past century since Marshall Hall's [31] concept that hibernation was a form of sleep differing from normal sleep only in degree, and in altering the irritability of the heart through diminution of respiration and a consequent change in the chemistry of the blood. Herrmann [34a] further studied the effect of small doses of sedative and antipyretic drugs in animals exposed to cold and noted that the toxicity of morphine, paraldehyde and certain of the barbiturates was greatly increased at low environmental temperatures, and that they caused a transient further drop in the body temperature. Magnesium chloride in non-depressant doses similarly has a hypothermic effect. It is interesting to note that aspirin produces no temperature drop except in the presence of actual fever.

Rosenthal [54] in studying picrotoxin and aconitine comes to the conclusion that there is a true "cooling" center located in the diencephalon and closely related to the centers controlling the parasympathetic system. No one man could possibly qualify nor does time permit digging into the fascinating but vast and complex field of temperature regulation, with its many ramifications into the related sciences: physics, engineering, chemistry, physiology and general biology. The names of Barbour of Yale, Bazett of Pennsylvania, Benedict of the Carnegie Foundation, DuBois of the Russell Sage Institute, and a host of others need only be mentioned as leaders in the medical aspects of this problem, to whose publications the reader is referred.

Other things being equal, in generalized hypothermy patients are made to all intents and purposes poikilothermic. It is true that this state is difficult, if not impossible, to attain in all patients unless preliminary sedation is used. However, small, non-depressant doses of drugs such as "Evipal" which act only briefly serve admirably to overcome the ordinary reflex reactions of shivering which occur chiefly while the temperature is falling to about 92° or 93° F. It is difficult for us to conceive of any prolonged narcotic effect of such sedation, as Herrmann [34] and others have intimated. Talbott [63] expresses the same point of view when he states: "Within an hour,

the anesthetic effect of the Evipal has for the most part worn off, and simultaneously the body temperature decreases. The anesthetic property of the cold usually obviates the necessity of further intravenous anesthesia or sedative."

If the effects of lowering the temperature inversely follow van't Hoff's law, then a reduction of body temperature of 10° to 12° C. from 37.5° C. to 23° C. or 24° C. should lower the rate of chemical and physical processes, viz., metabolism, to about half the former level. That figures approaching this theoretical level actually are attained can be shown by various physiological phenomena which occur while the patient is in that "profound oblivion midway between sleep and death" as Nuzie [48] expresses it in describing some carefuly controlled exxperiments on dogs, in which body temperature was reduced to 79.5° F. in the course of about six hours' exposure to an environmental temperature of 44° F. Basal metabolism in our series was reduced from 20 to 50 per cent although, as Talbott points out, part of this reduction may be attributable to intermittent sedation during treatment.

Many interesting physiological phenomena may be observed in the patient who is subjected to generalized hypothermy. Not the least interesting and important of these relate to the cardiovascular system. The heart rate tends to become slowed, although rarely below 50 beats per minute. The circulation time is prolonged, two or three times above normal. Blood pressure and the peripheral pulse may disappear entirely for hours at a time; constriction or collapse of the peripheral veins occurs, often rendering venipuncture impossible, but neither we nor others have ever observed actual thrombosis. Blood volume is presumably decreased as the result of a true anhydremia as shown experimentally by Harkins,[32] by Barbour,[6] and by DuBois,[21] the fluid being withdrawn into the interstitial spaces and even accumulating intracellularly as a mechanism designed to retain heat and thus reduce radiation. The volume output of the heart per minute is reduced. Evidence of this is seen in electrocardiograms in which the T-wave tends to become inverted or abnormal and in which there is a prolongation of the electrical systole. As Kossman [29] summarizes his experiences, decreased temperature is accompanied by a slowing of the pulse rate, a tendency towards lowering of the blood pressure, marked arterial, arteriolar and venous constriction, abnormality of the T-wave, the occurrence of auricular fibrillation above 85° F. and prolongation of electrical systole principally due apparently to a delay of the recovery process not related to alteration in the serum calcium. On the basis of observations of this character, and because of the occurrence of circulatory collapse and death either during the period of return of the temperature to normal or within a 24-hour period subsequently, in three or four instances, we had become somewhat concerned that myocardial degeneration was taking place because of anoxia resulting from the decreased cardiac output. It was not until an analysis of an equal number of terminal cases of malignancy that did not undergo refrigeration showed a slightly higher incidence of such circulatory failure and myocardial change

that we became convinced refrigeration was not in itself a serious risk to the average patient. From the practical standpoint of physiology it seems better to us for the patient to come out of his refrigeration state slowly, so that the load on his heart will not become suddenly too great. Likewise, is seems reasonable to give intravenous fluid during this period in sufficient amounts to compensate for the relaxation of the peripheral circulation which obviously takes place.

So far as the blood itself is concerned, we are likely to have an early hemoconcentration with a rise of the red cell count of anywhere from a quarter of a million to a million cells. There is usually a disproportionate leukocytosis up to as high as 15,000 or 20,000 and in occasional cases even to 40,000 or 50,000 cells. This rise is largely of the neutrophiles and disappears within a few hours after the temperature returns to normal. In cases that have been given several periods of refrigeration there is a tendency towards the development of a mild anemia, the result of disturbed maturation of the red cells from the cold. Likewise the leukocytosis is likely to be less marked in the fourth, fifth or subsequent refrigeration periods.

In a condition in which such profound changes occur clinically it is surprising that so little is found of an abnormal nature in the blood chemistry. There is no apparent significant alteration of the plasma proteins or A/G ratio. In our experience [59a] there has been no retention of nitrogen. In fact, in the majority of the cases studied there has been a definite tendency for the urea and non-protein nitrogen to fall even below the low side of normal. Vaughn [67] reported similar findings. On the other hand, Dill and Forbes [20] in their one fatal case noted such nitrogenous retention terminally. Blood sugar tended to drop, the average figure being between 80 and 90 mg., suggesting a resting state of the liver perhaps. Cholesterol and cholesterol esters appeared unchanged. No significant alteration in the calcium-phosphorus balance was noted. More attention should be paid to the other salts, especially potassium and magnesium, in subsequent studies. Carbon dioxide measurements were mostly within normal limits, although a few cases showed a little tendency towards the development of a very mild relative acidosis, which could be controlled readily by administration of glucose and fluids by mouth.

No impairment of renal function is apparent. If fluids are given, they are excreted with very little loss through respiration or the skin. Urinalysis has been regularly negative. Postmortem examination has not revealed any acute or other changes possibly attributable to refrigeration.

In general we have found it more satisfactory to withhold food during the refrigeration period except for small amounts of fluid and glucose, because the presence of food tends to activate the whole physiological mechanism and it is more difficult to maintain the temperature level desired. On the other hand the patient can be aroused, will swallow fluids and soft solids, although in many cases the swallowing reflex is poorly preserved.

Digestion seems entirely normal, although defecation during refrigeration is only rarely observed.

The one serious complication which we have seen in general refrigeration relates to the pancreas. Every now and then a patient develops a moderately severe acute pancreatitis. We have seen five such cases, and careful histologic study of all generalized hypothermy cases who have come to autopsy in the series reveals an incidence of minor inflammatory and degenerative changes of the pancreas in nearly 10 per cent. Daily blood amylase determinations during the refrigeration period should give adequate warning of impending disaster, and the patient's temperature should be restored to normal promptly to avert any serious complication. We have not yet been able to determine any particular reason for this discriminatory selectivity of the pancreas for trouble. Possibly its enzyme activity is not proportionally decreased as much as is the tissue resistance through relative anoxia from a diminished blood flow.

Curiously enough the respiratory rate is not usually altered much. The tendency is towards a gradual drop in rate to perhaps 12 or 14. In occasional cases it may fall to 8 or 10, and occasionally a rise to 28 or 30 may take place. The excursion is definitely reduced, so that breathing is "shallow" and ventilation correspondingly lowered. This apparently is a purely compensatory mechanism to match the reduced blood flow, for the color of these patients is essentially normal, without cyanosis. Because of the low temperature which is bacteriostatic for most of the ordinary upper respiratory bacterial flora, the development of pneumonia, although obviously presenting a certain risk, is no more likely to occur in a group of patients of this type than in the non-refrigerated cases. A terminal, patchy bronchopneumonia, which they felt was of no great importance, has been reported by Talbott [64] in the one fatal case in their series.

Subjectively, the mind is a complete blank from the onset of the induction period, except occasionally for a vague recollection of feeling cold as the temperature returns to normal through the "shivering zone" (92° to 97°). Exhaustive studies of the brain pathologically on more than 50 cases coming to autopsy following as many as seven and eight inductions have failed to reveal any demonstrable changes either grossly or microscopically.[55b] We had thought that with a slowed circulation we might encounter degenerative changes from cerebral anoxia, but there is absolutely no evidence, clinically or pathologically, of potential significance in so far as the application of general refrigeration in functional disorders of the brain is concerned. In this connection, it is of interest to note that the procedure has been employed by Talbott and his associates [63] in a series of schizophrenic patients with extremely gratifying results. It is of interest to us not only from the neurologic and psychiatric viewpoints, but because it represents what might be considered a normal control experiment for us in our work with terminal cancer cases.

Talbott [63] found that generalized hypothermia in schizophrenic patients under 30 years of age who had been sick for less than three years, with one exception, resulted in striking improvement which had been continuous for more than six months. In the older chronic cases no prolonged alteration in their mental symptoms occurred. Most of these patients had been treated previously with insulin or metrazol, or both, without benefit. He concludes that "with such promising results continued efforts in the use of hypothermy are thoroughly justified." In the one fatal case he states that there are three major trends in the acid-base balance of patients during hypothermia, i.e., hemoconcentration, acidosis, and retention of substances usually excreted by the kidney. This is accompanied by an alteration in the Ca/K ratio of the tissues, with Ca somewhat decreased and the K correspondingly increased. These various clinico-pathologic features are separately discussed in detail by Dill and Forbes.[20] They further conclude that prolonged hypothermia is without serious morphologic effect on the tissues.

Summary

From these somewhat disjointed comments regarding the biologic effects of cold on cell growth and differentiation and on mammalian physiology, it is hoped that the concept has emerged of the potential value of hypothermy in medical therapeusis. In spite of centuries of almost subconscious recognition of the usefulness of cold in the treatment of pain and fever, perhaps because of its very simplicity, its more extended use has only just begun to be explored. The brilliant work of Allen,[2] Crossman [3] and their associates in the peripheral vascular diseases and their associated surgery has pointed the way towards a new era for the diabetic and for military and civilian traumatic injuries of the extremities. The pioneering of Talbott [62] with generalized hypothermia in schizophrenia likewise opens the entire field of central nervous disorders to similar investigation. In our own work in malignant disease we believe we have conclusively shown the value of hypothermy in both localized and generalized application as an adjunct to other methods of treatment, and especially in the management of the terminal stages of the disease. Its value in the control of pain is often truly phenomenal and for this reason alone the method should be employed widely in a variety of pain problems. Its use in the treatment of narcotism seems well substantiated. Its value in the control of infections locally cannot be overemphasized. The clinical exploration of its value in a host of other pathologic states seems fully justified and urgently indicated. We must reëxamine our present concepts of physiology in the light of these new temperature levels attained, and successfully maintained by man. Perhaps it is not too much to hope that as our knowledge grows, it may be possible clinically to reach safely the "critical" levels of tumor cell growth which our tissue cultures suggest may well be destructive to cancer cells, and thus add an-

other truly effective weapon to the war against malignant disease. The evaluation of hypothermy as a therapeutic agent can only be attained by the combined efforts of the clinician and the laboratory man over a long enough period of time to discover its limitations as well as its usefulness. During this experimental period it is probably just as well that its more intensive application be limited to the larger institutions which have the facilities and personnel to carry out such investigative problems. In its present stage of development, like any other major therapeutic procedure—surgery, hyperthermia, even serum and chemotherapy—it is not without certain dangers, which must be recognized and methods designed to counteract them. These difficulties do not seem in the least insurmountable.

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THE SYSTOLIC MURMUR*

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THE systolic murmur is not an uncommon finding in routine examinations. Reid and Fahr have reported an incidence of as high as 20 and 35 per cent in normal youthful patients. The pendulum of opinion regarding the importance of these systolic murmurs has swung over a wide arc in the last century, from the extreme importance first attached to any murmur heard through the stethoscope to the view that murmurs were of no importance at all, and recently back again to viewing the systolic murmur with extreme suspicion. Mackenzie,[1] in his long continued follow-up studies, states that he has seen many individuals, with very loud rasping systolic murmurs for 30 years and with a rheumatic fever history, who never suffered from heart failure; and he states "where there are functional murmurs, the leak, if this be present causing them, is slight and never such as to embarrass the auricles in their work apart from cases where there is grave damage done to the heart muscle." He also says "the estimation of the sign of functional murmurs is not based on the murmur itself but on the functional efficiency of the heart and on the presence or absence of other signs of cardiac affections (size, rate, and rhythm)." From this point of view, there have been published recently many papers giving great importance to the systolic murmur. Thus Levine[2] claims "systolic murmurs do occur, but are not common in normal individuals" and, after classifying these murmurs according to loudness from class one to class six, states "the loud ones are always associated with some form of cardiovascular disease." He includes, in a series of 1000 cases, all systolic murmurs even if complicated by conditions which would, as Blumgart[3] pointed out, cause a murmur because of the increase of the velocity of the blood stream, such as a severe anemia, hypertension, and hyperthyroidism. On the other hand, R. C. Cabot[4] pointed out that without other signs of cardiac disease the systolic murmurs are of no importance as evidence of valve lesions and claims "a diagnosis of mitral regurgitation without stenosis is never justified." Other investigators[5, 6, 7, 8] have reported varying views with reference to the importance attached to this condition.

A very confusing factor is the reliance to be placed on insurance statistics, which have led most insurance companies to conclude that there is no such thing as a functional murmur and on that basis to rate up heavily or reject for life insurance an applicant with a murmur. F. H. McCrudden,[9] in a recent article, states that there is a definite decrease in life expectancy with apical systolic murmurs. In a recent review of 2,100,000 insurance

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cases from 1909 to 1927 inclusive, the conclusion is reached that there is a tremendous increase in the mortality rate of all cases with a systolic murmur except those in which the murmur is at the pulmonic area, soft, inconstant, and not transmitted.

Fineberg and Steuer[10] analyzed 100 cases presenting a systolic apical murmur which they had observed over a period of years. They concluded that in youngsters with a systolic murmur and a history of rheumatic fever or chorea there is a 50 per cent chance for the development of mitral stenosis, aortic regurgitation or both, that mitral stenosis or aortic regurgitation appeared on the average three to four years after the first observation, and that in only eight instances did the murmur disappear. Recently, however, the same authors reported the observation for over 10 years of 35 of the original 100 patients without the discovery of any new cases of mitral stenosis or aortic regurgitation.

In the series of cases we are now reporting we have taken only those in whom there is no associated disease which might have caused the murmur and only those in whom careful physical examination, vital capacity, electrocardiographic, orthodiagraphic, and laboratory studies convinced us that the heart was normal in spite of the presence of a systolic murmur. In this series were also included those cases with a history of rheumatic fever or chorea. In concluding that there was a systolic murmur present, we defined the systolic murmur, as did Freeman and Levine,[11] as a " distinct bruit that is heard definitely following the first sound and extending appreciably into systole." We did not group them according to loudness, but in this series there were murmurs of varying intensity. In other words, this is a study of the pure systolic murmur as such and as evidence of an embarrassing valve lesion. Approximately 23 per cent of the cases referred to the Cardiac Clinic for cardiac examination were called normal and about 25 per cent of these normal cases had a systolic murmur. We were not interested in the significance of this systolic murmur as regards pathologic lesions of other organs. We have studied a group of 100 cases (not consecutive) with systolic murmurs over a period of from four to 16 years, ranging in age from 12 to 71 years. In the first 100 consecutive cases, we were able to get a return of 72 and were unable to trace the remaining 28. Of these 28 whom we could not trace, the Minnesota State Board of Health reports that there have been five deaths with two dying of pneumonia, one postoperatively, one of ruptured appendix, and one of melanotic carcinoma.

Of the 100 cases (not consecutive), 28 had a definite history of from one to three attacks of rheumatic fever or chorea occurring from three to 27 years before the first examination by us. A great majority of them had been restricted in activity before coming to the clinic and many had been given cardiac medications. The average follow-up period was about seven years. The murmur was located at the apex in 44 cases and at the base or sternum in the remainder. Electrocardiograms were taken on all cases and were negative. Every case also had an orthodiagram and esophagogram.

Bardeen,[12] checking the relation between heart volume, transverse diameter and area, found that their interrelation was sufficiently constant to justify the use of transverse diameter and area as indicative of heart volume. In determining the heart size in this series the measurements of the heart were limited for practical purposes to the transverse because, as pointed out, measurement of area frequently involves, besides the experimental error in obtaining heart outline, a further error in measuring it. Variations in the position of the heart were corrected by correlation with body height, weight, and age, and by comparison with the predicted transverse normal as obtained by the formula of Hodges and Eyster,[9] which can predict that diameter with an error of less than five mm. (the transverse diameter of the heart $= + 0.1094 \times$ age $+ 0.8179 \times$ weight $- 0.1941 \times$ height).

Assuming that after a follow-up period of this length of time, the heart, if embarrassed by a valve defect of any consequence, should certainly show some signs of cardiac disease besides the systolic murmur and an increase in heart size of measurable degree, the findings of the last examination were compared with those of the first. In these 100 cases we found, after an average period of seven years, 96 showing no significant changes in electrocardiograms, orthodiagram, vital capacity, esophagogram, or physical findings. The standard deviation in these 96 cases seen in a large cardiac clinic in the orthodiagram studies was only 5.4 mm. An increase beyond the predicted transverse normal, as determined by the formula of Hodges and Eyster,[9] as well as any marked increase in this diameter beyond the first measurement, was considered abnormal. It bespeaks the extreme accuracy of carefully done orthodiagraphy that no more care was taken in the fluoroscopic examination of this group of patients than of those routinely examined in the cardiac clinic. After this follow-up period of seven years, we have the following four cases who, at the last examination, had developed definite heart abnormalities besides the systolic murmur and now showed definite cardiac findings.

Case Reports

Case 1. This woman was first seen in 1933, was 20 years old, 5 ft. 5½ in. tall, and weighed 114 lbs. Family history was negative. She gave no cardiac symptoms, but there was a history of chorea at the age of 11. The only cardiac finding was a systolic murmur at the base, moderately loud, not transmitted, and not affected by breathing or exercise. No diastolic murmur was heard. Vital capacity, electrocardiogram, and esophagogram were normal. Orthodiagram showed the heart to be normal in shape with a transverse measurement of 9.7 centimeters. When examined in 1938 this patient still had no symptoms. The systolic murmur was then heard at the apex and was transmitted to the axilla. There was still no diastolic murmur. Vital capacity was still normal but electrocardiogram now showed a tendency to right preponderance and the heart had increased 3.1 centimeters in transverse diameter to 12.8 centimeters. The transverse thoracic measurement was 21.8 centimeters. The esophagogram was still negative. We now consider this a case of possible pure mitral regurgitation.

Case 2. This case is that of a young girl aged 15, 5 ft. 6 in. tall, weight 115 lbs., who was first seen in 1932 with no cardiac symptoms, a negative family history, and a

negative history of rheumatic fever. The only finding was a systolic murmur at the apex, constant but not transmitted. There was no diastolic murmur heard. The vital capacity was normal. The electrocardiogram showed a tendency to left preponderance but was otherwise negative. The orthodiagram revealed a normal shaped heart though with a slight fullness of the conus area which is sometimes seen in a drop type of heart. The esophagogram was negative. The transverse diameter was 11.9 centimeters. When seen again, in 1934, the findings were the same and there were no cardiac symptoms. The electrocardiogram, however, now showed a tendency to right preponderance, and the orthodiagram revealed a transverse heart diameter of 12.6 centimeters. The patient was seen again in 1938 and had shown a further increase of the transverse diameter to 13.3 centimeters, with a transverse thoracic measurement of 23 centimeters or a total increase in six years of 1.4 centimeters. The esophagogram has been negative at all times and no diastolic murmur has ever been heard. We now believe this to be a case of possible mitral regurgitation.

Case 3. This patient was a man aged 25, 5 ft. 8¼ in. tall, weight 173 lbs., first seen in 1931. He had a negative family history, but gave a history of rheumatic fever at the age of 18. The only cardiac finding, when he was first seen, was a systolic murmur at the base, not constant and not transmitted. Electrocardiogram, vital capacity, orthodiagram, and esophagogram were normal. The transverse diameter of the heart was 12.5 centimeters and the transverse thoracic diameter 25.5 centimeters. Five years after this examination this patient had another attack of rheumatic fever. When reëxamined in 1938, this man had developed not only a systolic murmur at the apex but a typical mitral-diastolic murmur. He still had no cardiac symptoms. His vital capacity was still normal, but his esophagogram was now positive to the right and to the posterior. The transverse diameter of the heart had increased 1.4 centimeters to 13.9 centimeters. He had a definite conus bulge with a typical mitral shaped heart. We believe that the last attack of rheumatic fever, in 1936, damaged the mitral valves.

Case 4. The fourth patient was a woman aged 41, 5 ft. 3¾ in. tall, weight 153 lbs., first seen in 1931. She gave a negative family history, negative history of rheumatic fever, and had no cardiac symptoms. The only cardiac finding was a loud constant systolic murmur at pulmonic area. Vital capacity was normal, as were orthodiagram and electrocardiogram. The orthodiagram revealed a normal shaped heart with a transverse diameter of 11.75 centimeters with a transverse thoracic diameter of 24 centimeters. When this patient was examined in 1938 she still had no cardiac complaints. The vital capacity was still normal and the systolic murmur was the same, but on orthodiagram the transverse diameter of the heart was definitely increased by 1.4 centimeters to 13.1 centimeters. Electrocardiogram now showed a flat T_2 and a negative T_3. Her blood pressure had remained 130 mm. Hg systolic and 86 mm. diastolic. We now believe that this patient has developed coronary disease.

It would be reasonable to assume that, even with a rheumatic history, if these cases showing systolic murmurs had a valve lesion which would affect their heart efficiency to any appreciable degree, some finding other than the heart murmur should be elicited in the period of time covered. Beyond the cases stated this was not true. In one case coronary disease developed; and we believe only two cases really had a mitral insufficiency at the time of first diagnosis, as the heart in the other case was probably damaged by a later attack of rheumatic fever. It is also interesting to note that the hearts which later showed cardiac findings other than the systolic murmur were followed for a period of six and one-fourth years and showed very marked increases in heart size whereas the others did not. It is important

to note that of the four cases reviewed which developed demonstrable heart lesions in addition to the murmur only two had a history of rheumatic fever; and that these cases which did not develop definite signs of cardiac pathologic lesions did not have a history of rheumatic fever within a period of at least three years prior to the first examination or thereafter. The only case in which a diastolic murmur could be heard at the second examination was one in which the patient had had a new attack of rheumatic fever two years before the last examination.

Conclusion

We did not try to diagnose conditions in organs other than the heart by the systolic murmur, but in spite of the fact that these cases of systolic murmur were not consecutive, we believe a vast majority of them were normal hearts as far as functional capacity is concerned and that "if we find in a heart of normal size and rhythm a systolic murmur with absence of any sign that would indicate that it is definitely organic in origin and with a good functioning organ, then we may conclude that the heart is perfectly normal. If there be evidence of weakness or other signs of abnormal conditions present, then the opinion should be based on these other signs and not the murmur."

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POLLEN IN OIL: A PRELIMINARY REPORT ON A NEW, SLOWLY ABSORBED MEDIUM FOR USE IN HAY FEVER TREATMENT*

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DUNBAR, in 1905, was the first to attempt pollen desensitization against hay fever. He injected horses with crude pollen, then bled the animals and used the serum on hay fever patients. It is very obvious that this treatment was unsuccessful because of horse serum reactions, and the method soon fell into bad repute.

Noon, in 1911, was the first to place desensitization on a scientific basis by preparing an aqueous extract of timothy pollen. This work was further elaborated by Freeman, Koessler, Scheppegrell and Clowes. Glycero-saline extracts are still claimed to be the most stable, but when used in 50 per cent concentration of glycerine and injections of 3 per cent pollen are given to patients, they are very irritating and painful. This has been a serious drawback to its use in 3 per cent concentration.

Extracts of pollen in 5 per cent glucose have overcome this objectionable feature, but like all aqueous extracts the greatest obstacle is the rapidity of absorption with its consequent local and general reactions. Spain and Sammis, in 1935, used ultrafiltered extracts and reported more successful desensitization.

Harrison, in 1934, studied the effect of alum precipitated pollen extracts on guinea pigs. He felt that the addition of alum might slow down absorption and allow for the use of higher concentrations of pollen.

Caulfield, Brown and Waters added alum as an adjuvant in sensitizing guinea pigs to ragweed pollen. They were successful and reported that sensitization was produced more readily by this method.

Keeney, Pierce and Gay were the first to prepare epinephrine in oil. The epinephrine was suspended in sterile peanut oil. This has been a great advance in the treatment of asthma because of the slow absorption and consequent sustained action of the epinephrine.

For a number of years poison ivy and oak extracts in oil have been used both prophylactically and therapeutically with excellent results for ivy and oak dermatitis.

In view of these attempts to use oil extracts it occurred to one of us (S. J. T.) that if pollen could be prepared in oil such a mixture could be used to great advantage in the treatment of pollinosis.

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The technical preparation of this mixture was undertaken with the assistance of Dr. S. O. Levinson of the Serum Center of Michael Reese Hospital.

It is generally known that many patients will have both severe local and constitutional reactions from the usual aqueous pollen mixtures. The large number of injections required both preseasonally and perennially often are objectionable to many patients. The patient who presents himself for treatment during the pollen season has always been a problem. The rapid method of desensitization with the resulting rapid absorption occurring with aqueous solutions has been a source of severe reactions and a serious drawback to that method of therapy.

Technic of Extraction of Pollen in Oil

An aqueous 3 per cent pollen extract solution was frozen in a carbon dioxide, carbon tetrachloride mixture and evaporated to dryness in vacuo. The residue was then redissolved in sterile sesame oil. As the solubility of the residue is slight, it is necessary to leave it in contact with the sesame oil at room temperature for six days. Aerobic and anaerobic cultures of the sesame oil-pollen extract mixture showed no bacteriologic growth after seven days' incubation at 37° C.

There have been no reports of sensitization to sesame oil. Sensitization to peanut oil and poppy seed oil have been frequently reported. Sesame oil can be easily sterilized in an autoclave for 15 minutes at 15 pounds of pressure. It has a low specific gravity and runs easily through a 27 gauge needle.

Intradermal tests were made on 200 ragweed sensitive patients and delayed positive reactions resulted in all of them. Reactions consisted of erythema and itching coming on 30 minutes after the intradermal test. Small pseudopods were present in some patients. Control tests with sesame oil were negative. By this method it was possible to produce a 20 per cent pollen mixture, and intradermal tests made with this concentration merely resulted in a larger area of erythema and more marked itching coming on about 30 minutes after the test. In a few patients itching persisted for 24 hours following the test but the erythema persisted for one hour. Further observation revealed that, after a quiescent period of one week, there is a reappearance of the reaction consisting of a raised red papule with itching, again indicating the slowness of absorption. No constitutional or marked local reactions occurred with the 20 per cent pollen in oil mixture in any patient. Dry pollen is suspended with difficulty in any oil; however, after lyophilization the active principle is not altered in any way and is more easily suspended in oil. It can be kept at room temperature without deterioration.

Conclusions

1. The active principle is present in these oil extracts as evidenced by the local reactions produced in sensitive individuals.

2. A slower rate of absorption is demonstrated, with less likelihood of severe local and systemic reactions.

3. Higher concentrations of pollen extract are possible with pollen in oil and, therefore, patients can be given a single large dose with no danger of constitutional reactions.

4. These extracts do not deteriorate at room temperature and need not be refrigerated.

5. We are reporting this preliminary work because we feel that pollen in oil has such tremendous possibilities, not heretofore obtainable with aqueous extracts.

A report on its use in patients with hay fever symptoms will be made at a later date.

Note: Since this article was written in June 1941, the lyophilized pollen and the sesame oil have been homogenized rather rapidly by the use of an electric homogenizer. The active extract does not separate out, on standing in this oil mixture, and a perfect homogenized mixture results.

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SOME PHYSIOLOGICAL OBSERVATIONS ON THE CIRCULATION DURING RECOVERY FROM VITAMIN B_1 DEFICIENCY *

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Observations on the cardiovascular disturbances accompanying vitamin B_1 deficiency in man have accumulated rapidly during the past decade. Aalsmeer and Wenckebach [1] and Keefer [7] described the cardiac form of beriberi occurring in the Orient. Scott and Herrmann [12] found similar cases of cardiac failure among the rice cultivators of Louisiana who developed the "maladie des jambes" each autumn when the diet consisted of polished rice and bacon grease.

Minot, Strauss and Cobb [9] recognized the importance of nutritional deficiency and especially deficiency of vitamin B_1 in the etiology of "alcoholic" polyneuritis and compared this condition to beriberi. A few years later Weiss and Wilkins [17] reported a number of cases of cardiac failure associated with nutritional deficiency, described the syndrome, and called attention to its relative prevalence in the western countries among those addicted to alcohol. Since then, there have been numerous reports, some on isolated cases, others on series of cases, all of which have been comprehensively reviewed by Weiss in a recent article.[16] In this he sums up the evidence in favor of a causative relation between thiamin deficiency and the cardiovascular dysfunction of berberi.

Of the total number of contributions to this subject during the past 12 years, only a small fraction have been concerned with this syndrome from the standpoint of circulatory dynamics. Studies made by Weiss and Wilkins [17] demonstrated that in heart failure from beriberi the circulation time is *decreased,* an observation which points to an increase in the velocity of blood flow, and that the arteriovenous oxygen difference, as measured by blood samples taken simultaneously from femoral artery and vein, is diminished, which suggests an increase in the volume of flow. The venous pressure was elevated in some of their patients. Weiss and Wilkins concluded from these and other studies that the circulatory disturbance accompanying beriberi is caused in the main by a combination of arteriolar dilatation and myocardial failure.

Prior to the work of these authors, Hayasaka and Inawashiro [5] made studies on the minute volume of patients with beriberi using the original ethyl iodide method of Henderson and Haggard.[6] In the light of Starr and Gamble's [13] later work, their figures are probably too high, but they may be

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relatively significant, and the conclusion that the cardiac output in beriberi is increased is strongly suggested by the figures they present. These investigators also believed that relaxation of the peripheral vessels was the chief cause of the increased minute volume. These physiological observations of Hayasaka and Inawashiro and of Weiss and Wilkins indicate that circulatory failure in beriberi is somewhat different in mechanics from that caused by the more common etiologic factors such as hypertension, rheumatic valvular disease and coronary artery disease. Moreover, the disordered functions leading to congestive heart failure in beriberi are more nearly reversible than those usually present in other forms of heart disease.

The present paper reports further measurements of the circulation in vitamin B_1 deficiency. It is based on observations of two patients with such deficiency, carried out during their recovery from congestive cardiac failure. The observations include repeated determinations of the cardiac output, arterial and venous pressures, circulation time, and oxygen consumption. In one patient several determinations of the blood volume were made. All determinations were made under standard basal conditions. Oxygen consumption was measured with the Tissot spirometer. The cardiac output was calculated by means of the acetylene method of Grollman[3] using the three sample procedure suggested by Grollman, Friedman, Clark and Harrison.[4] The venous pressure was measured by the direct method of Lyons, Kennedy and Burwell.[8] The circulation time was determined by the "Decholin" method of Winternitz et al.[18] The blood volume was measured by the method of Gibson and Evans.[2]

On one patient (J. L.) venous pressure, circulation time and vital capacity measurements were made on the day of admission before any specific therapy had been started. Thiamin was first given that evening, and on the following morning the blood volume and oxygen consumption were determined. On the second day after therapy was started the first cardiac output determination was carried out. On the other patient (R. J.) thiamin was started the day before admission and was continued without interruption until recovery was practically complete. The initial venous pressure reading was taken on the second hospital day, and the vital capacity and circulation time were measured on the following day. On the fifth hospital day the first cardiac output was determined.

It should be emphasized that these studies in no way represent the complete picture of the circulatory changes in B_1 deficiency. Because of technical difficulties and the serious condition of the patients, it was not possible to carry out all of the observations until after B_1 therapy had been instituted. Moreover, recent animal experiments indicate that vitamin B_1 deficiency is a relative state: an active animal may be in deficiency on a given vitamin intake whereas at rest with the same intake, adequate vitamin B_1 may be present to satisfy the demands. Hence although no additional vitamin has been given, the animal may no longer be deficient, in fact may be in a state of repair. Both these patients had been at rest in bed for several days pre-

ceding our studies. For this reason, it is impossible to judge the exact state of deficiency in these two patients at the time the studies were instituted. However, we believe that our observations are of interest in throwing some light on the problem of B_1 deficiency and present them here with the reservations mentioned above.

Case Reports

Case 1. J. L., a 32-year-old unemployed married male, was admitted to the Peter Bent Brigham Hospital on June 6, 1940, with the complaint of puffiness of the face and swelling of the ankles. For many years the patient had indulged in week-end sprees. During the past year the alcoholic intake had gradually increased up to two or three pints of wine and a quart of ale daily. When financial straits prevented the purchase of these beverages, rubbing alcohol and other cheap substitutes were used. About six months before admission he began to feel "rum sick" in the morning. His appetite became poor, and frequently he ate but one meal a day. Three or four months prior to entry it was noticed by the patient and others that his face looked puffy, and a month or so later he first noticed swelling of his legs. At the same time he experienced tenderness in the calves of his legs and the soles of his feet on walking. One month before admission he noticed shortness of breath on walking several blocks. Two weeks before entry he developed red scaling lesions on the dorsal surface of both hands. At this time his face and eyes were very puffy, there was marked increase in ankle edema, and he was unable to walk across the street because of dyspnea.

His only illness in the past had been one attack of what was said to be rheumatic fever at the age of 10.

Physical examination at the time of admission revealed an irritable, confused, puffy-faced male with strong alcoholic odor on the breath. The rectal temperature was 98° F., the pulse was 120, and the respirations were 24. The skin was warm and moist. Over the dorsal surfaces of both hands were erythematous, pigmented scaly lesions and similar lesions were present in the suprapubic region extending almost to the umbilicus. The pupils were dilated and reacted sluggishly to light. The tongue was large and thick but not abnormally red or smooth. There was no cyanosis and no distention of the neck veins. The cardiac dullness was enlarged to percussion and measured 11 cm. to the left of the midsternal line in the fifth interspace and 3 cm. to the right in the fourth interspace. The rhythm was regular. The heart sounds had a tic-tac quality, and at the apex a short, blowing murmur was present late in systole. The blood pressure measured 128 mm. of mercury systolic and 84 mm. of mercury diastolic. The lungs were clear of râles. The liver was felt 4 cm. below the right costal margin in the midclavicular line. Edema of the ankles, legs and sacrum was present. The positive findings on neurological examination included increased deep reflexes, marked sensitivity of the soles of the feet, tenderness of the calf muscles and coarse tremor of tongue, hands and feet. There were no delusional trends or hallucinations at the time of admission.

At the time of admission the red blood cells numbered 3,520,000, the white blood cells 7,800. The hemoglobin was 78 per cent by the Sahli method. The urine had a specific gravity of 1.008; it contained no albumin or abnormal sediment. Wassermann and Hinton reactions of the blood serum were negative. The blood nonprotein nitrogen, sugar and icterus index were normal. The serum albumin and globulin in grams per 100 c.c. were 4.0 and 2.8 respectively. The serum ascorbic acid was 0.1 mg. per 100 c.c. (The normal range in this laboratory is from 0.4 to 1.5 mg. per 100 c.c.) A roentgenogram of the chest on the day following admission was interpreted as showing enlargement of the heart, chiefly to the left, and a marked increase in the lung markings. Fluoroscopy showed a heart beat of good amplitude. Electrocardiogram showed normal complexes and left ventricular preponderance.

Therapy with thiamin chloride and nicotinic acid was started about 24 hours after admission. Recovery from the state of obvious congestive heart failure present on admission took place rapidly. On the fourth day of hospital stay the pitting edema of the legs and ankles had disappeared, although some puffiness about the eyes persisted. At this time the systolic murmur had also disappeared. The leg tenderness, unsteadiness of gait and tremor improved more slowly, but the patient was able to be up in a chair on the ninth day in the hospital. At this time the lesions of the hand had entirely cleared up. His weight decreased from 67 kg. on admission to 57 kg. three weeks later on the day before discharge, and during this time his appetite and food intake increased greatly. Associated with the loss of weight there was a progressive rise in the red blood cell count and hemoglobin content toward normal values. Serial roentgenograms of the heart demonstrated a progressive decrease in size first apparent on the fifth day in the hospital. Normal dimensions were attained on the eleventh hospital day. Three weeks after admission the patient was discharged essentially well. The diagnoses were: beriberi, beriberi heart with cardiac insufficiency, alcohol addiction, delirium tremens, and pellagra.

The patient was readmitted to the hospital on October 4, 1940, complaining of burning of his feet and slight tenderness of his calves of two weeks' duration. He stated that, since discharge, he had continued to take two to five pints of wine and some beer and ale daily. He had eaten very little food and for the past five weeks had discontinued the Brewer's yeast tablets prescribed on his discharge. His symptoms gradually became so severe that he was unable to walk so he returned to the hospital. Examination revealed marked tremors of his hands, hyperesthesia of his feet, and paresthesia of his soles. His blood pressure was 170 mm. Hg systolic and 120 mm. diastolic. There were no evidences of cardiac dysfunction on this admission. He was treated with thiamin chloride 10 mg. four times daily, Brewer's yeast 5 gm. daily. His symptoms disappeared and he left the hospital against advice on October 19, 1940. The diagnoses were: alcohol addiction and polyneuritis.

Case 2. R. J., a 23-year-old taxi driver, was admitted to the hospital on March 2, 1939, with the complaint of inability to use his legs, of five days' duration. For the past six years he had consumed about one-half pint of whiskey a day and during the past three months had increased this to one pint a day. This increase in consumption was apparently related to economic difficulties and personal maladjustment. He had noted a gradual disappearance of his appetite and for the past two months had subsisted on one cup of coffee and one to two sandwiches a day. During the three weeks just preceding admission he had had anorexia and he had vomited daily for two weeks. He began to notice progressive lameness in his legs and swelling of his feet. There was also some numbness and tingling in the fingers of his left hand in addition to generalized weakness. Five days before admission, he became much more irritable, "jumpy," and nervous. His condition became so alarming that he was taken to the Psychopathic Hospital where he had an attack of delirium tremens with typical tremors, overactivity, hallucinations and disorientation.

At that time he was found to have cardiac enlargement, edema, absent knee and ankle jerks, tenderness in the muscles of the arms and legs, great weakness of the arms and legs with coarse tremors and nearly complete paralysis from the waist down. With sedation and nursing care, he became mentally clear on the following day, but remained in the institution, where he was given a high vitamin diet, Brewer's yeast (8 gm. t.i.d.) and, on March 1, 1000 units of thiamin chloride subcutaneously and 300 units by mouth. He continued to be mentally clear, but his other disabilities persisted. After four days he was transferred to the Peter Bent Brigham Hospital on March 2, 1939, for further therapy.

Physical examination on admission revealed a very hyperactive, irritable, nervous young man complaining bitterly of pains in his legs. His temperature was 97.2° F., and respirations were 24. Pulse was 104, and blood pressure was 124 mm. Hg systolic

and 62 mm. diastolic. The skin was flushed, warm, and moist. The heart was moderately enlarged to percussion, and the heart sounds were loud with a suggestion of embryocardia. A high-pitched blowing systolic murmur and a systolic gallop rhythm were heard at the apex. A soft systolic murmur was heard over the aortic area. The pulse was fast and felt full and bounding. Moderate venous distention was visible in the neck. The lungs were clear. The liver was enlarged to percussion and somewhat tender. There was moderate pitting edema of the calves and marked pitting edema of both ankles. There was marked weakness and incoördination of all muscles of the legs without any obvious atrophy and no specific muscle paralysis. All the muscles of the thighs and calves were exquisitely tender to palpation, and there was marked tenderness along the peripheral nerves, especially the sciatic nerve. Motion in all joints was limited by extreme muscle sensitivity and weakness. There was numbness and partial objective anesthesia to light touch of the left forearm, the palm of the left hand, and the fingers.

Laboratory data on admission were: erythrocytes, 3,740,000; hemoglobin, 72 per cent; leukocytes, 7,300 (with normal differential distribution); Hinton and Wassermann reactions were negative. The urine showed no significant abnormalities. Phenolsulphonphthalein excretion was 66 per cent in two hours. The non-protein nitrogen of the blood was 57 mg. per 100 c.c.; the total protein 5.7 gm. per 100 c.c.; the albumin 2.9 and the globulin 2.8. A seven-foot film of the chest showed moderate cardiac enlargement, both to the right and left, with a rather straight left border. There was fairly marked pulmonary congestion around the hila and in the right base. The electrocardiogram showed normal curves.

The patient was placed on a high caloric, high vitamin diet with thiamin chloride, 12 mg. subcutaneously daily and Harris yeast tablets, 4 gm. t.i.d. Under this therapy, there was rapid and dramatic improvement in the patient's condition. He ran a moderate temperature elevation (101° F.) for several days. By the third hospital day he was practically free from pain and was able to move his legs without hurting himself. Several days later no murmurs or gallop rhythm were audible over the heart, and by the tenth hospital day all edema had disappeared, and the patient was quite comfortable and able to sit up for short periods during the day. Erythrocytes and hemoglobin rose to normal values, and the non-protein nitrogen level returned to normal. Subsequent films of the chest revealed progressive decrease in the size of the heart and clearing of the lung fields. By the eleventh day of hospitalization, the heart was normal in size to roentgen-ray examination. Electrocardiograms continued to be normal except for some increase in the size of the T-waves. His improvement continued, and he was allowed increasing periods of walking, first with assistance and then alone. On his discharge March 30, 1939, 28 days after admission, the patient was able to walk fairly well, but exhibited considerable atrophy of the intrinsic muscles of the hands and forearms with moderate generalized atrophy of the muscles of the legs. He still had a moderate tachycardia. During the period of hospitalization his weight decreased from 71.6 kg. to 58.6 kg. Most of this weight loss occurred during the first two weeks and could be explained for the most part by loss of edema fluid.

The patient was readmitted to the hospital on April 23, 1939, for observation. He had continued on Brewer's yeast daily and Harris yeast tablets 1 gm. t.i.d. plus three teaspoonfuls of cod liver oil daily. He showed considerable improvement, was able to walk upstairs easily, and had noted a gradual disappearance of his limp. He had gained weight and felt well.

Physical examination revealed a fairly well nourished, calm individual. The skin was dry and cool. The heart and lungs were normal. The blood pressure was 115 mm. Hg systolic and 60 mm. diastolic, and the pulse rate varied between 100 and 110. The liver was somewhat increased in size to percussion, but was not tender. There was slight weakness of the legs. There was moderate tenderness to palpation in

TABLE I

Patient 1 (J. L.)

Date	Oxygen Consumption C.c. per Minute	Basal Metabolic Rate	Arteriovenous Oxygen Difference C.c. per Liter	Cardiac Output: Liters per Minute	Cardiac Output: C.c. per Beat	Cardiac Output: Liters per 100 C.c. Oxygen Consumed	Cardiac Output: Liters per Square Meter of Surface Area	Basal Heart Rate per Minute	Venous Pressure Mm. H_2O	Circulation Time Seconds	Vital Capacity C.c.	Weight Kg.	Arterial Pressure Mm. Hg	Blood Volume C.c.	Therapy
6/ 7/40									195	13.6	2500	67.1	128/84		10 mg. thiamin chloride
6/ 8/40	268	+17						87		13.0				Plasma 3830 Red blood cell 2350 Total 6180 Hematocrit 37.9%	20 mg. thiamin chloride
6/ 9/40	293	+28	63.0 61.4	4.71	49.1	1.61	2.85	89							20 mg. thiamin chloride
6/10/40									85			60.3			10 mg. thiamin chloride daily
6/11/40	280	+21	70.8 64.0	4.15	43.2	1.80	2.50	101		18.0	2900				
6/12/40	246	+ 8						90		15.0	3000				
6/13/40	289	+24	73.5 75.4	3.88	38.8	1.34	2.35	95				60.5	130/98		
6/14/40	282	+23	70.2 72.8	3.95	41.1	1.40	2.39	94				59.5			
6/17/40	259	+13						95	50	15.5	3000	58.5			
6/18/40	257	+13	76.1 70.4 70.0	3.56	37.1	1.39	2.16	93					124/90		
6/21/40									58	18.3		57.7		Plasma 2450 Red blood cell 2110 Total 4560 Hematocrit 46.3%	
6/26/40	242	+ 6	70.4 76.9 77.4	3.23	33.7	1.34	1.96	90			3050	57.3	122/92		Thiamin chloride discontinued
7/ 2/40	243	+ 5						82	65	26.5 24.7	3200	57.8	140/110		
7/ 5/40	227	− 2	70.9 75.8	3.09	32.2	1.36	1.88	83				56.7	126/90		

TABLE II

Patient 2 (R. J.)

Table II

Patient 2 (R. J.)

Date	Oxygen Consumption C.c. per Minute	Basal Metabolic Rate %	Arteriovenous Oxygen Difference C.c. per Liter	Cardiac Output				Basal Heart Rate per Minute	Venous Pressure Mm. H_2O	Circulation Time Seconds	Vital Capacity C.c.	Weight Kg.	Arterial Pressure Mm. Hg	Therapy
				Liters per Minute	C.c. per Beat	Liters per 100 c.c. Oxygen Consumed	Liters per Square Meter of Surface Area							
3/ 2/39													124/62	
3/ 3/39									260			71.6		12 mg. thiamin chloride daily
3/ 4/39									235	13.8	2000			
3/ 5/39									210 198		1800			
3/ 6/39									123					
3/ 7/39	303	+33	33.8 30.9	9.80	86.0	3.23	5.80	102						Thiamin chloride discontinued
3/ 9/39	296	+26	54.6 57.0	5.30	50.0	1.79	3.14	106				71.4		
3/12/39											3400		124/96	
3/13/39	264	+13	48.9 51.2	5.27	45.4	2.00	3.12	114				60.2		
3/14/39										15.8		60.2		
3/15/39	245	+ 5	56.8 57.0	4.31	38.5	1.76	2.55	112						
3/17/39	250	+ 7						112				58.6		
3/18/39													140/104	
3/19/39											3700			
3/25/39													116/92	
3/28/39	234	± 0	54.1 56.3	4.05	38.9	1.73	2.40	104		14				
3/30/39								100						
4/19/39	247	+ 5	67.1 68.6	3.64	36.4	1.47	2.15	100				61.0		
4/24/39									46	28				
7/ 5/40	227	− 2	70.9 75.8	3.09	32.2	1.36	1.88	83				56.7	126/90	

the calf muscles. Routine laboratory studies were not remarkable. The patient was discharged on April 24, 1939, with instructions to continue his medication. The diagnoses were acute alcoholic hallucinosis, beriberi (alcoholism), beriberi heart with cardiac insufficiency and neuritis due to beriberi.

The measurements of the circulation in these two patients are set forth in tables 1 and 2, and graphically represented in figure 1.

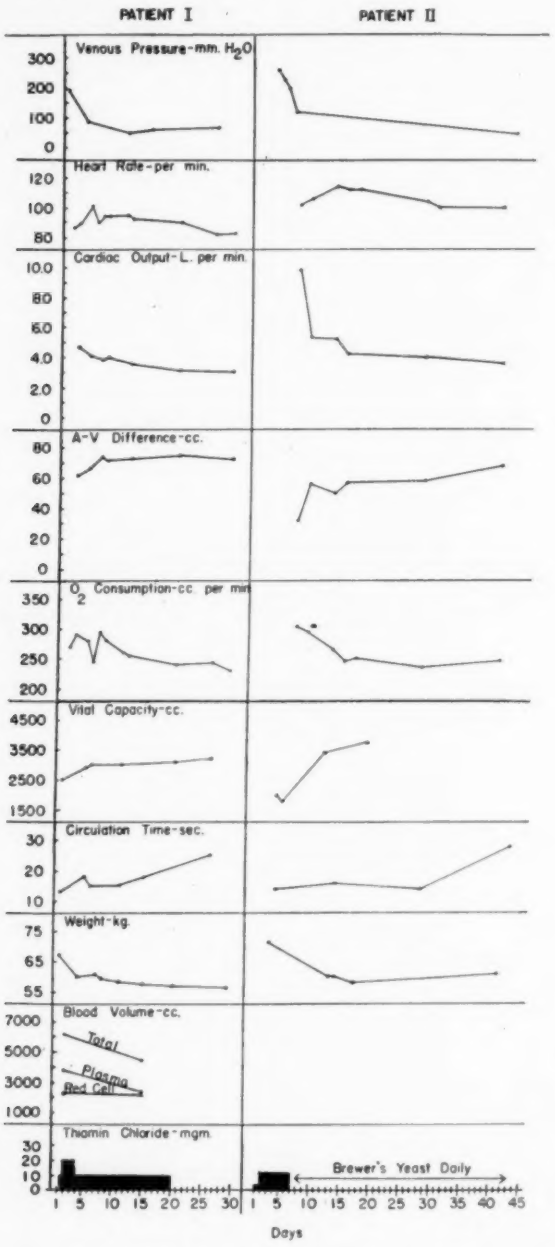

FIG. 1. Measurements of the circulation in patients 1 and 2 in relation to therapy.

Discussion

It is evident that both patients at the time of admission had frank congestive heart failure. This is concluded from the combination of elevated venous pressure, dependent pitting edema, reduction in the vital capacity, and roentgen-ray evidence of cardiac dilatation and pulmonary congestion. In neither case could the extensive edema be attributed to hypoproteinemia although in one the albumin was moderately reduced. The signs in each pointed to failure of both the right and the left ventricle, though predominantly the former.

Our observations bear out those of others that during congestive heart failure associated with vitamin B deficiency there may be an increased cardiac output, a low arteriovenous oxygen difference, an elevated venous pressure, and a shortened circulation time. During recovery there is a change toward normal of these measurable circulatory phenomena, viz., a decline in cardiac output, an increase in the arteriovenous oxygen difference, a fall in venous pressure and a prolongation of the circulation time. In addition, in one patient (Case 1), it was shown that during failure there was a marked increase in the plasma and total blood volume, both of which returned to normal during recovery. We also found in both patients an initially high oxygen consumption which likewise gradually returned to normal under observation. It may be argued that this high oxygen consumption accounted for the high cardiac output values, but the fact that the arteriovenous difference was abnormally low indicates that the cardiac output was increased out of proportion to the metabolic needs of the body. Roentgen-rays of the heart shadow in both cases showed the dimensions considerably increased beyond normal before therapy. Beginning a few days after the start of therapy there was a progressive decrease in the size of the heart shadows which gradually returned to normal limits within two weeks (figures 2 and 3). The electrocardiograms in both patients revealed essentially normal complexes at the beginning of observation and no definite change following therapy.

Although the initial value for the cardiac output was well above the average normal in patient 1 and in patient 2 was about twice the upper limit of normal, our data do not permit us to state with certainty that the cardiac output in either patient was above normal during the interval between admission and the time of our first observations. It would be of interest to have data on the cardiac output during this period because from the observations that we have at hand we are unable to say how much, if any, our initial measurements were modified by the short period of treatment preceding them. Other investigators have suggested from direct measurements of the cardiac output and indirect observations (accelerated circulation time, hot flushed skin and bounding pulse) that congestive failure occurring in vitamin B_1 deficiency is associated with a cardiac output that is above normal. It was likewise observed in our patients that the circulation time

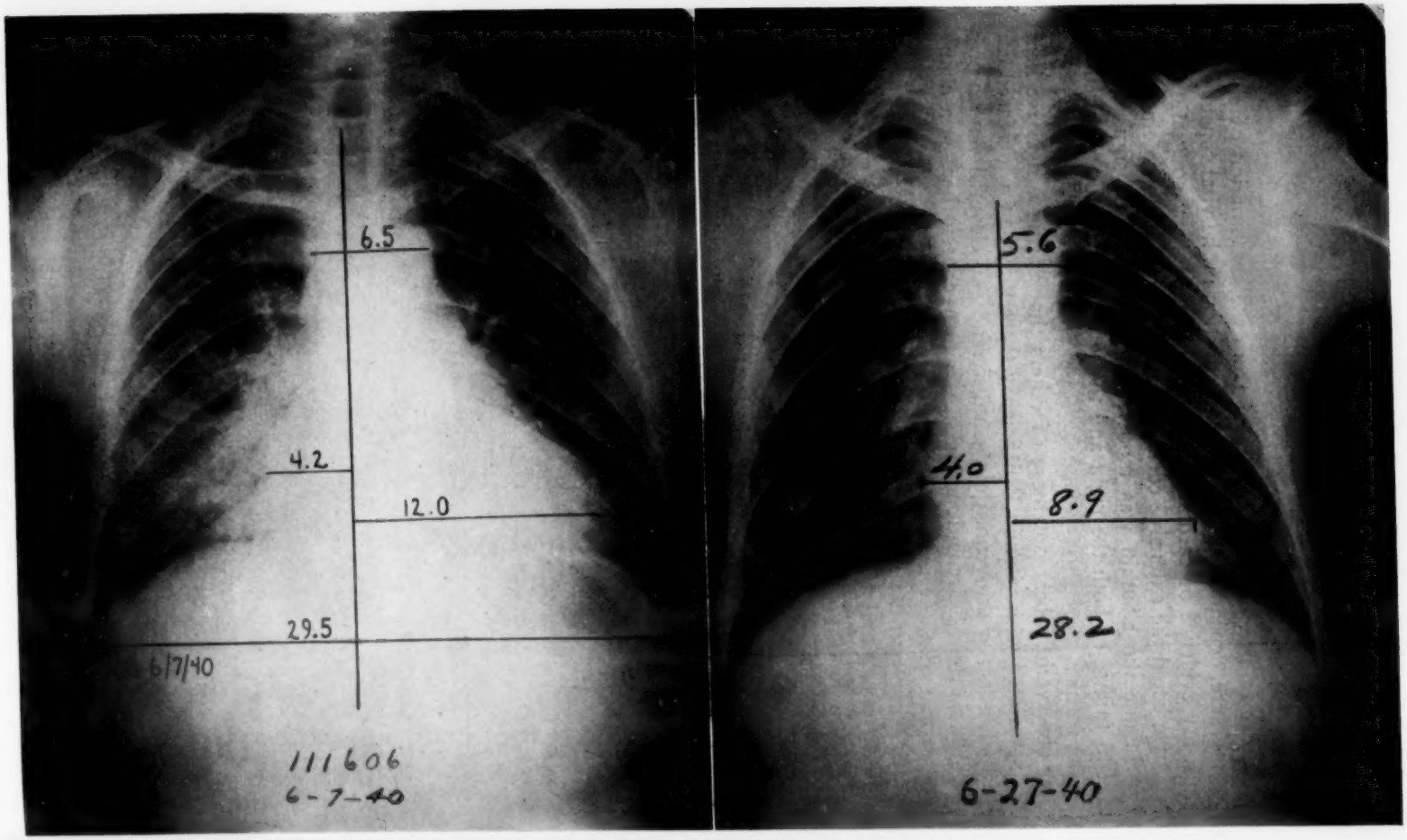

FIG. 2. Roentgenograms of patient 1 on admission and 20 days after treatment was begun.

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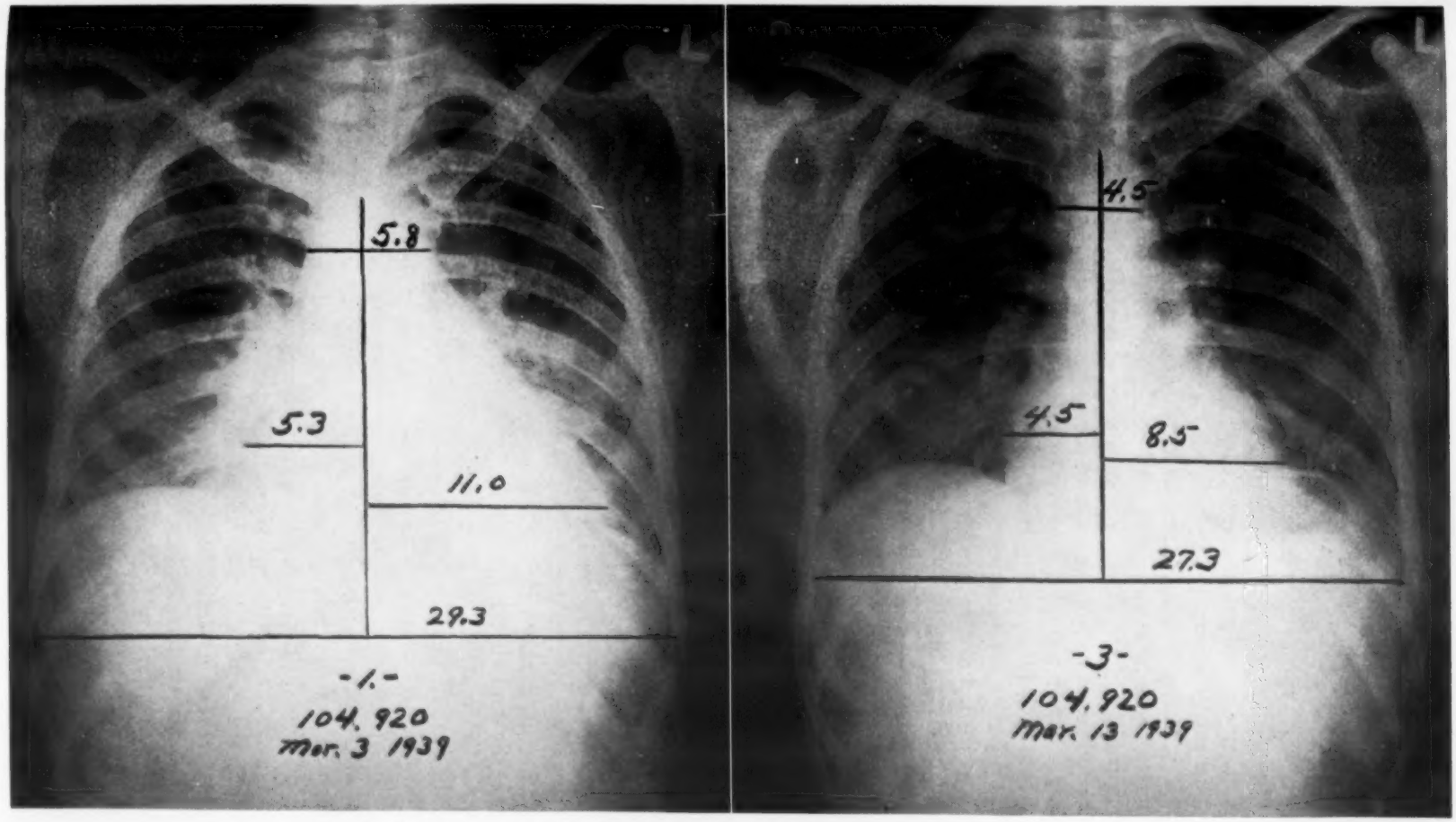

FIG. 3. Roentgenograms of patient 2 on admission and 10 days after treatment was begun.

was shorter during failure and that as recovery took place the circulation time became prolonged. It is probable, then, that the initial determinations of the cardiac output in our patients represent the approximate levels present before therapy was begun, but it must be admitted that these values may have been elevated to some extent by a further increase immediately following the start of therapy.

It is probable that recovery from heart failure due to B_1 deficiency is brought about by a combination of decreasing cardiac load and a more efficient myocardium. The elevation of systolic and diastolic blood pressure, the decrease in pulse pressure, and the slowing of the circulation which were observed after therapy was started are evidences that an increase in arteriolar tone took place during recovery. Weiss and Wilkins[17] postulated that "arteriolar constriction following B_1 therapy must also react, in turn, centrally on the heart in the same beneficial manner as the closing of an arteriovenous aneurysm." Theoretically this change may bring about a decrease in the minute volume of blood returning to the right heart and hence would reduce one major factor in the amount of work required of the heart. Actually, such a decrease was observed. At the same time it is suggested by animal experiments and pathological material[11, 14, 15] that thiamin deficiency may directly affect the myocardium, resulting in less efficient function and even failure at levels of work ordinarily handled with ease. Thus, it is probable that the administration of thiamin in our patients acted directly on the heart and that the action is to some extent responsible for the disappearance of the phenomena of congestive failure.

The finding of an initially elevated oxygen consumption which gradually returned to normal levels is subject to two interpretations. One is that the oxygen consumption is elevated in vitamin B_1 deficiency, and that our observations represent a gradual return to normal under therapy. The second is that, during deficiency, oxygen consumption is at a low normal level or below and that immediately following therapy there is a sudden and marked increase in this function and that our initial figures were determined at the peak of this rise. The only study of this function in human beings[5] shows higher values during deficiency than after therapy and hence favors the former hypothesis. However, in one of our patients (Case 1), on two occasions there was a definite rise in oxygen consumption after the institution of therapy, reaching a peak on the third and sixth days of therapy. In the other patient, measurements of the oxygen consumption were not made until after the fourth day of treatment and this may account for the failure to observe the initial rise. In addition, experimental work on isolated tissues[10] reveals a diminished oxygen uptake in deficiency and an increased metabolism on the addition of thiamin, and studies on the pigeon[14] and other animals show that oxygen consumption is decreased below normal during vitamin B_1 deficiency. These findings would tend to substantiate

the second hypothesis of compensatory increase in oxygen consumption following therapy. It is apparent that this problem needs further investigation before a definite conclusion can be reached.

Summary and Conclusions

Observations related to certain circulatory functions were made on two patients recovering from cardiac failure associated with vitamin B_1 deficiency. These observations showed increased cardiac output (with both a decreased arteriovenous oxygen difference and an increased oxygen consumption), elevated venous pressure, accelerated speed of circulation and, in the one patient in whom the determination was made, increased blood volume. These altered circulatory functions were observed to return to normal during the recovery period.

These observations are in accord with opinions expressed by others that the cardiac output is increased during congestive failure associated with vitamin B_1 deficiency. The observations suggest, furthermore, that one important factor leading to recovery from this type of cardiac failure is contraction of an abnormally dilated peripheral vascular bed.

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TULAREMIA

A REPORT OF THREE FATAL CASES WITH AUTOPSIES *

By H. B. THOMAS, M.D., F.A.C.P., *York, Pennsylvania*

THE purpose of this report is to submit clinical and pathologic studies of three fatal cases of ulcero-glandular tularemia, two of them being of the rapidly fatal primary septicemic variety and the third of longer duration.

The first fatal case with autopsy was reported in 1924 by Verbrycke [1]; and since then about 60 additional autopsy studies have been published.[2] Duplications in the literature make it difficult to state the exact number of necropsy cases.

CLINICAL PICTURE

The incubation period varies from a few hours to 13 days, but it is usually from two to five days. In the cases reported below the primary sore or constitutional symptoms appeared within five days. In 90 per cent of the cases a primary lesion develops at the site of inoculation as a small papule which rapidly enlarges and ulcerates leaving a punched-out ulcer with a necrotic floor. There is usually a primary bacteremia which persists for seven to 10 days and results in the formation of focal necroses in the lung, liver, spleen and lymph nodes. Regional lymph node involvement results from the direct extension of the organisms along the deep lymph channels, resulting in enlargement of these nodes in 90 per cent of the cases. Occasionally, as in two of our series, this primary bacteremia is a septicemia from the onset in an individual who has little or no natural resistance, resulting in death within 14 days.

This primary bacteremia usually disappears as antibodies are developed. Likewise, the areas of necrosis in the lungs, liver, etc., heal with scar formation as resistance appears. As most deaths occur at a later stage and on the basis of considerable cultural and necropsy evidence, Foshay, Francis, and other leading students of the disease have postulated that there is a second blood stream invasion in the majority of the fatal cases. This septicemia arises from any one of the previously established areas of necrosis by ulceration into a blood vessel or by direct invasion from the lymph tissue to the blood stream. This septicemia results in the production of countless areas of necrosis which may appear in any organ, but chiefly in the liver, spleen, lungs, and lymph nodes.

The onset is frequently abrupt with chills, fever, sweats, headache, malaise, and various gastrointestinal symptoms. Great prostration is the rule. The primary lesion with regional adenopathy is present at the onset or ap-

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pears in 24 to 48 hours. This lesion is most often found on the fingers or hand but may appear on any part of the body coming in contact with the invading *Bacterium tularense*. Visible lymphangitic streaks appear only when there has been secondary infection of the primary lesion. Fever is always present and averages 102° to 104° F.; its duration in uncomplicated cases is from two to four weeks. When complicated by pneumonia or suppurating buboes it may last several months. Cough is an early and tran-

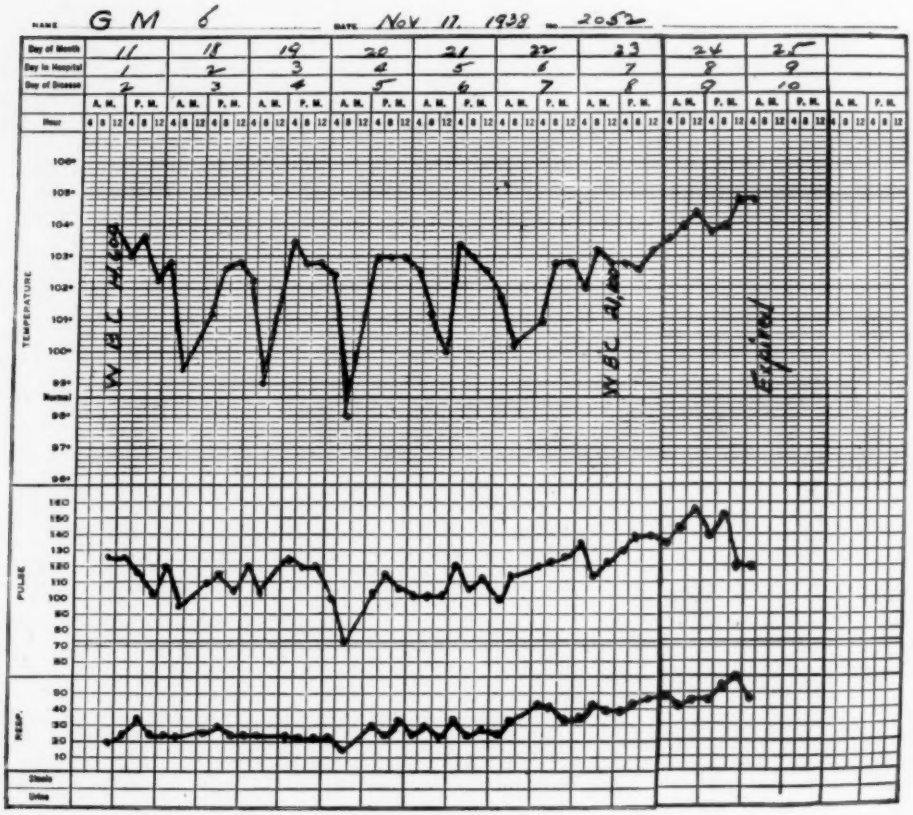

FIG. 1. Clinical chart of Case 1. Note the leukocytosis and evidence of severe infection. Duration of illness 10 days.

sient symptom and disappears by the second week. Clinical signs of pulmonary lesions occur in at least 18 per cent of the cases and about an equal number develop pleural effusions. Pulmonary signs may be present at the onset of the disease, but more frequently they appear after the initial symptoms. The physical signs are variable; they appear and disappear from day to day unless the process has become massive. Usually both lungs are affected but the signs are, as a rule, more marked on one side than on the other. At first the signs may be those of capillary bronchitis with the presence of fine crepitant râles and the absence of definite areas of dullness. As

the lesions progress, patches of impaired resonance with coarser râles will be found. As the process coalesces, actual dullness with tubular breath sounds is noted. These changes, as portrayed, are extremely variable. The course may be fulminating and terminate fatally in a few days or progress slowly over a period of weeks. If recovery occurs, the signs clear very slowly, persisting for a long time after constitutional symptoms have disappeared.

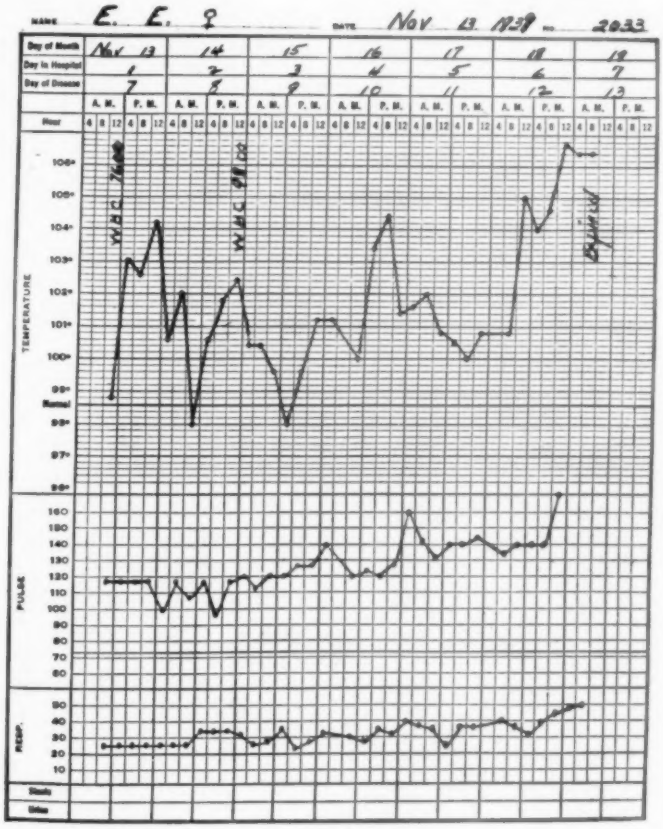

FIG. 2. Clinical chart of Case 2. Note the absence of leukocytosis.

Pleural effusion may occur at the onset, but more frequently appears during the course of the infection. The effusion may or may not be associated with intrapulmonary involvement. The fluid is exudative in character with lymphocytes predominating in the cell count. The *Bacterium tularense* has rarely been demonstrated in the fluid, but it may cause agglutination of the organism in high dilutions. With pleural fluid occurring alone at the onset of the disease the difficulties in differentiating this disease from tuberculosis are obvious.

Besides capillary bronchitis, bronchopneumonia, and lobar pneumonia, the process may present the signs of lung abscess. For a period of a week or more there may be a single area of moderately impaired resonance with

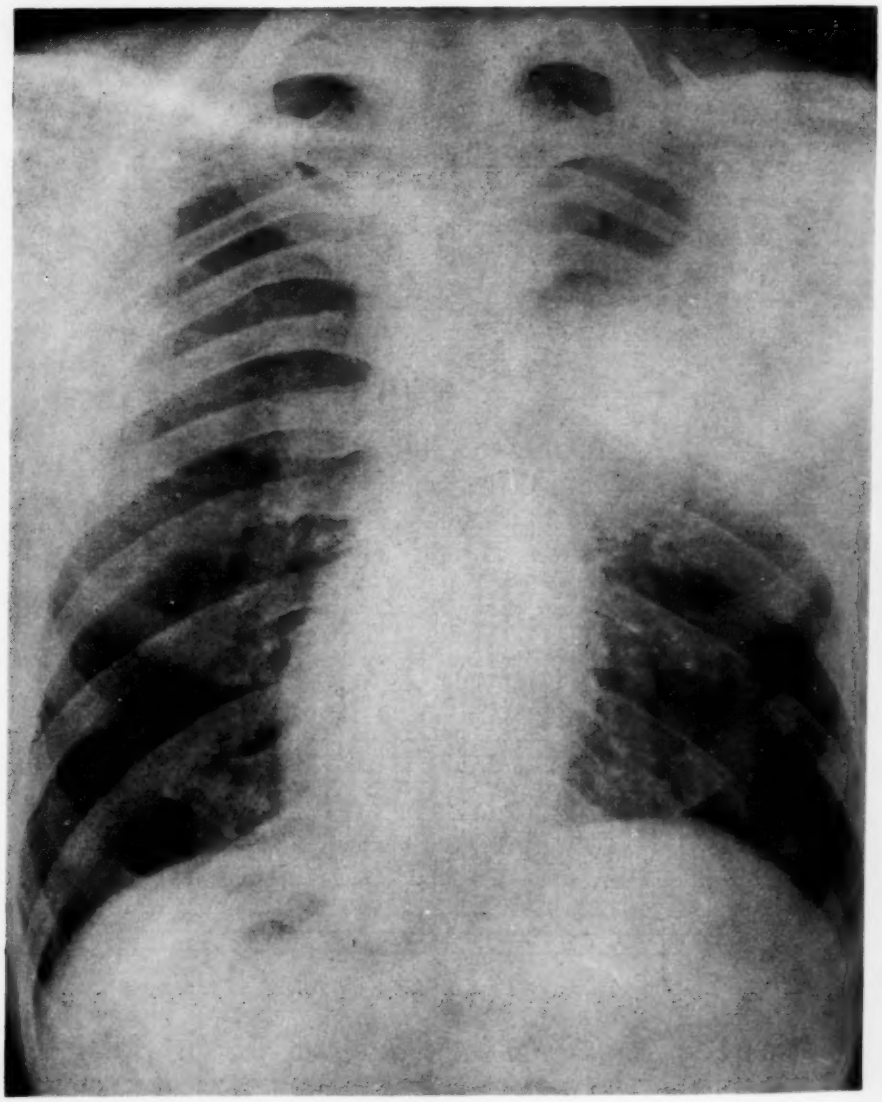

FIG. 3. Roentgenogram of chest of Case 3, showing pulmonic consolidation in upper right lobe.

harsh or definitely tubular breath sounds, and roentgenograms may present the typical picture of a solitary abscess. This lesion may progress to cavity formation or slowly regress. If the disease progresses slowly throughout both lungs the signs may be those of multiple cavitation.

Recovery occurs in approximately 94 per cent of the cases but the convalescence is often prolonged over a period of months even in the absence of complications.

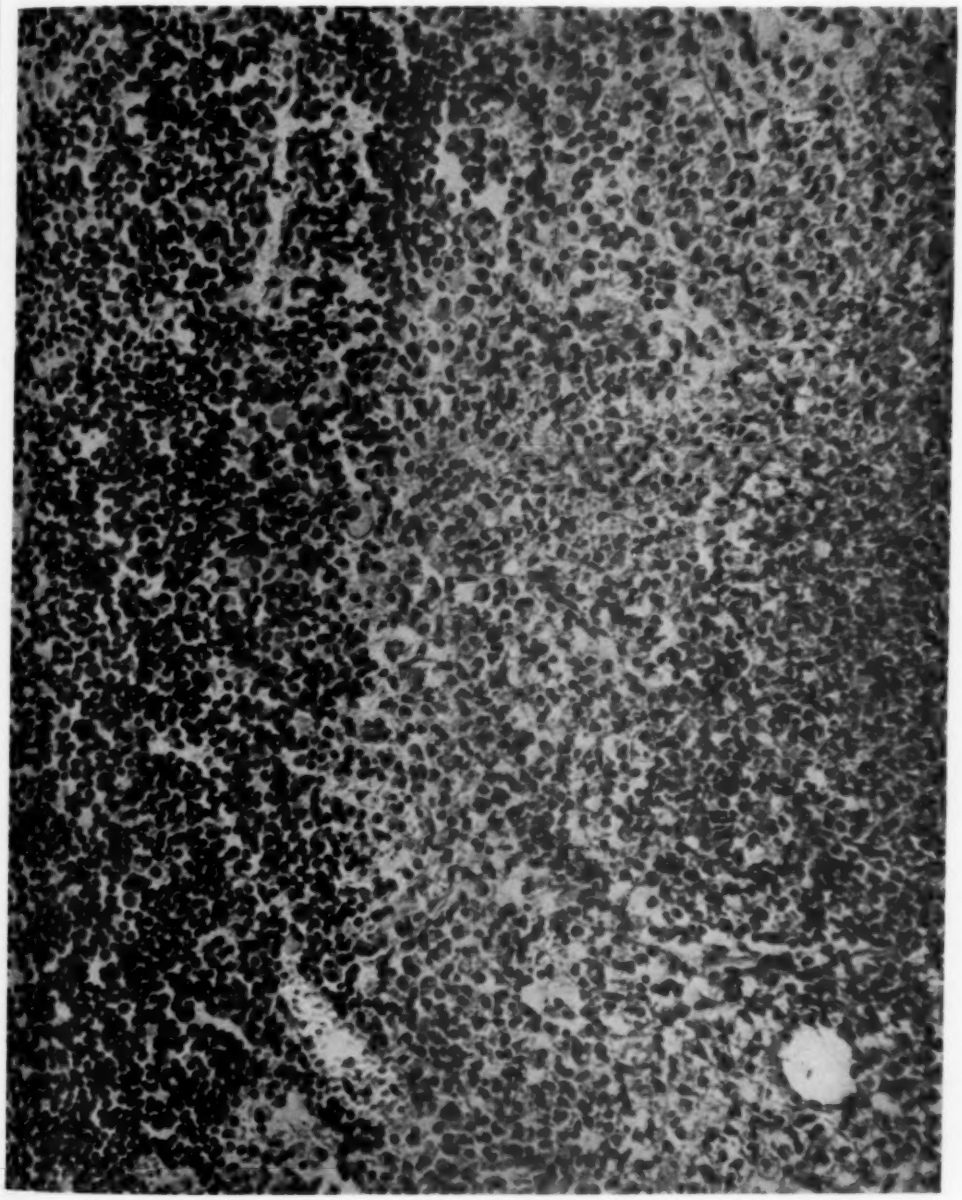

FIG. 4. Axillary lymph node demonstrating the margin of an area of coagulative necrosis. This is an early stage in which the nuclei in the necrotic area covering the right three-fifths of the illustration exhibit pyknosis and karyorrhexis, whereas viable hyperplastic lymph nodal tissue constitutes the left two-fifths. Note absence of encapsulation. Ten days after onset.

The clinical features seen in patients with a primary septicemia are somewhat different from those of the average case in which the individual develops a degree of immunity. Man possesses very little natural immunity but is usually capable of developing protection in time to prevent his destruc-

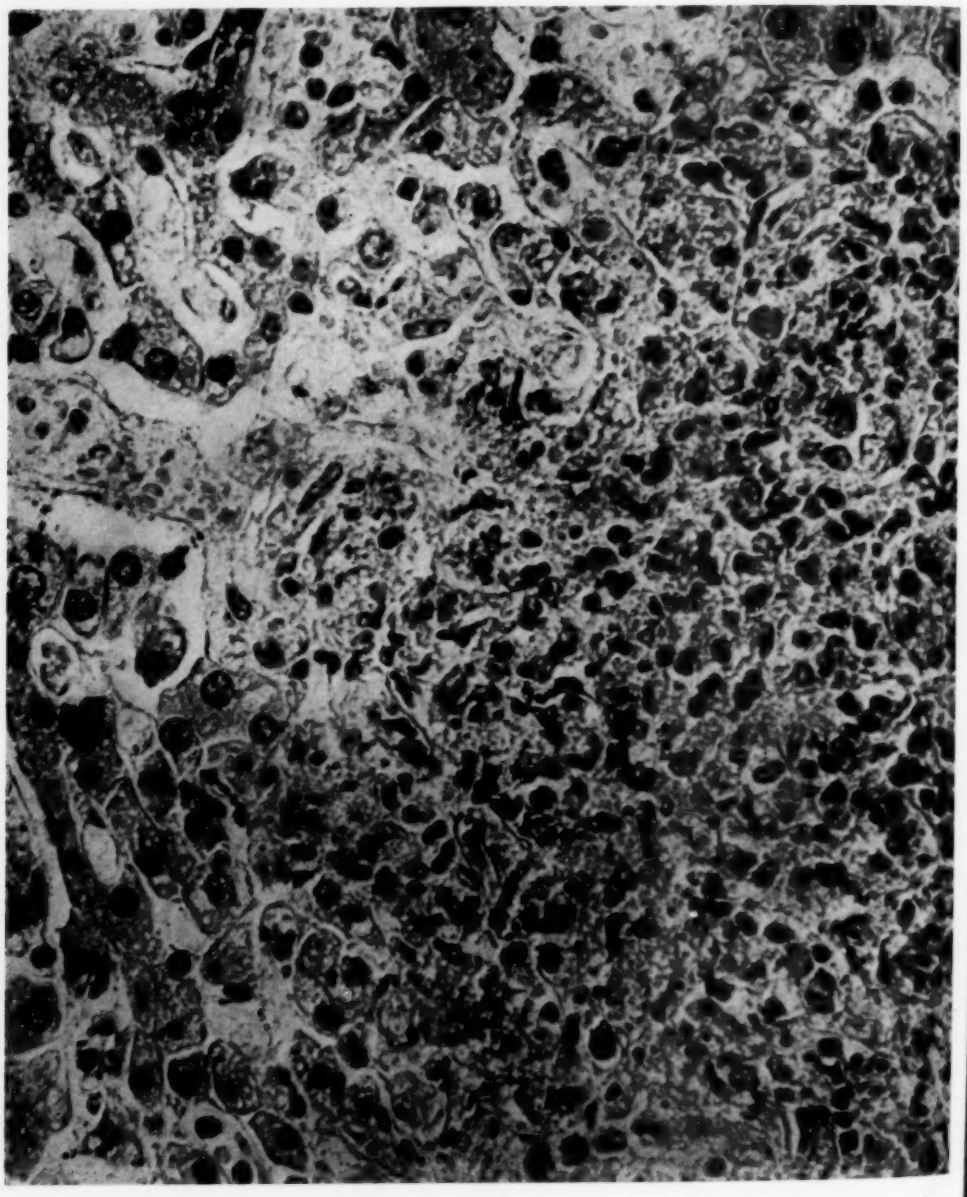

FIG. 5. Liver. A focal necrosis in which the debris of disintegrated hepatic cells is mixed with lymphoid cells and histiocytes which have wandered into the area, most of which are pyknotic or fragmented.

tion. There is, however, a small percentage of individuals who cannot develop this protection and therefore succumb to tularemia within a fortnight or less, as is characteristic of the disease in rodents. In this group the primary bacteremia is maintained as a septicemia until the victim dies. A patient with a primary septicemia has the usual incubation period but with the onset of clinical symptoms becomes desperately ill with great rapidity. There are repeated drenching and debilitating sweats following the sharp chills. The fever curve presents either marked fluctuations or maintains a high level. The patient is prostrated, and there is severe malaise. Usually there is marked tympanites, slight jaundice, slight splenomegaly and hepatomegaly. Cyanosis and a slight cough herald the approach of pulmonary involvement which frequently progresses to bronchopneumonia. Delirium occurs early, and the patient rapidly progresses to coma and death. Other findings that occasionally occur are diarrhea, renal changes of hemorrhagic nephritis, and inflammation of the peritoneum, pleura, and pericardium.

The diagnosis of tularemia is established by culture of the primary lesion, blood culture, agglutination studies and by skin tests; however, at times it is exceedingly difficult to demonstrate the presence of the causative organism, particularly in the rapidly fatal cases. Culture of the primary lesion is unsatisfactory at times because of partial healing or secondary invasion of contaminating organisms which obscure the *Bacterium tularense*. This organism grows slowly, frequently requiring four days for recognition. This factor adds to the difficulty of making the diagnosis by means of blood cultures because in the severe septicemias the patient may die before growth appears. Agglutination tests do not become positive before the second week and frequently much later. The chief advantage of the agglutination test is that it becomes positive in 100 per cent of cases and persists for many years after recovery. A titer of at least 1 : 80 is necessary for diagnosis unless there has been a previous negative agglutination. Cross agglutination with *Brucella abortus* and *Bacillus proteus* OX–19 may cause some difficulty in rare instances. Huddleson's phagocytic test is of value in those instances in which this cross agglutination with the Brucella group occurs. Foshay[3] has described antigen and antiserum skin tests. The former is ideal from a diagnostic standpoint and is now commercially available. The antiserum test is claimed to have the same high accuracy as the antigen test (100 per cent positive before agglutinins appear) but this point is disputed by Friedewald and Hunt.[4]

Pathologic Studies

The internal organs most frequently and severely affected by the invasion are the lymph nodes, lungs, liver and spleen.

The structure of the involved lymph nodes varies with the stage of the disease. Hyperemia, edema, reticuloendothelial hyperplasia and aggrega-

tions of lymphocytes, plasma cells and macrophages in the sinuses lead to a loss of distinction between sinuses and medullary cords in the earlier stages. Here, too, areas of coagulative necrosis and karyorrhexis, beginning in the cellular aggregates within the sinuses, extend to constitute grossly apparent

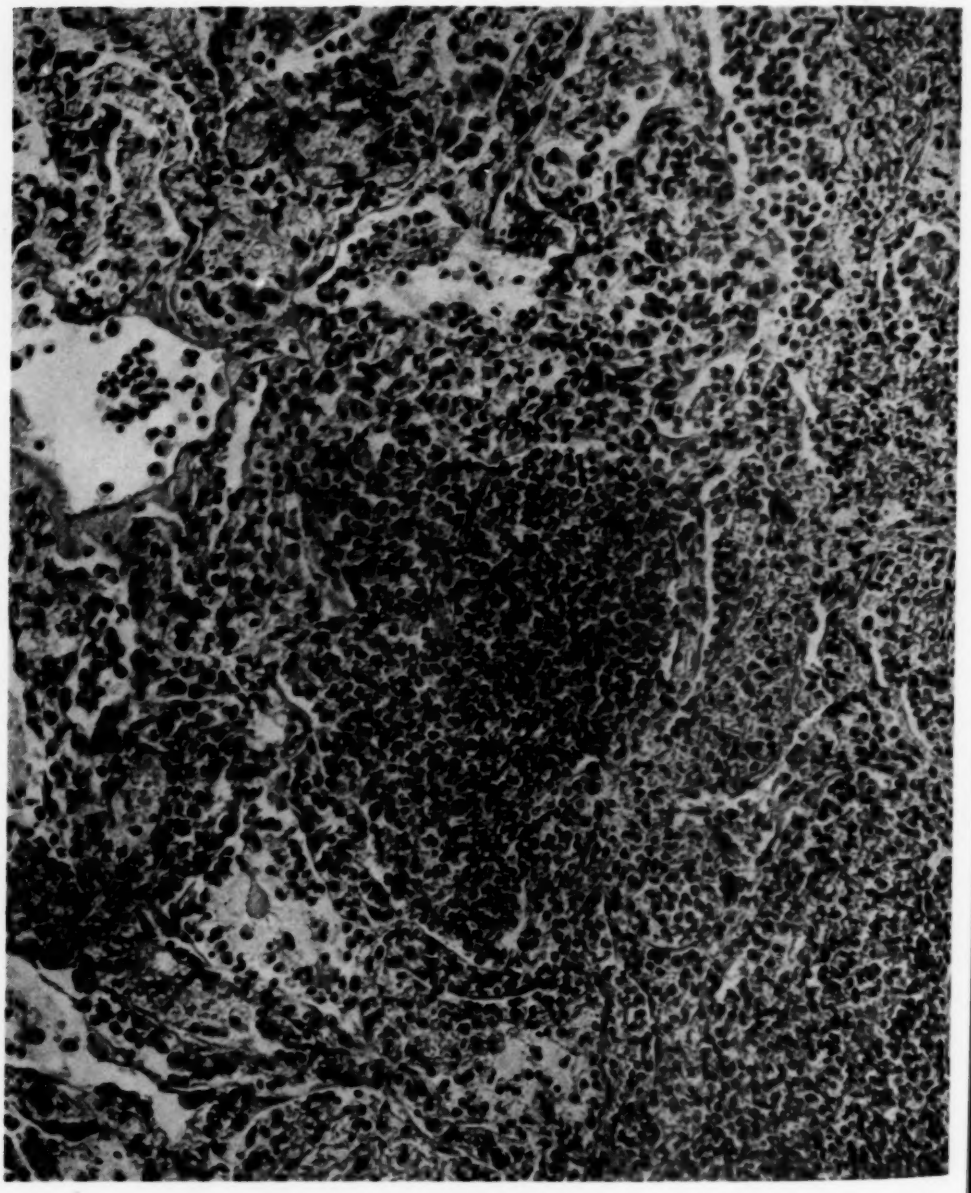

FIG. 6. Lung. This shows beginning coagulative necrosis. An intra-alveolar exudate of lymphoid cells and macrophage histiocytes is undergoing pyknosis and karyorrhexis. Later it will be represented by dense amorphous debris which, with the further disintegration of alveolar walls (here begun), will comprise bulky areas of necrosis, grossly caseous.

areas of caseation. Vascular thrombosis, areas of hemorrhage, fibrin and polymorphonuclear leukocytic exudation (this infrequently) may be found. Progression of the disease is accompanied by encapsulation of the areas of necrosis by epithelioid cells, often in palisade-like arrangement, with lymphocytes and various histiocytes peripherally; and in this cellular periphery one or more multinucleated cells may be found, often with a mural distribution of nuclei. Replacement of the epithelioid cells by fibroblasts, which proceed to form a fibrous wall about the areas of caseous necrosis, marks the later stages.

Pulmonic lesions are present in over 90 per cent of the fatal cases, with involvement of one or more lobes. Although occasionally of lobar distribution, they are usually focal or confluent. Two general types of lesions are described: pneumonic and localized caseous necrosis. However, areas of necrosis can be found within pneumonic areas, and it is possible that all tularemic pulmonic lesions have a common pathogenesis, that all areas of localized necrosis develop as a progressive coagulative necrosis of intra-alveolar exudate and alveolar septa. This exudate is chiefly of monocytes, lymphocytes, histiocytes and plasma cells, polymorphonuclear leukocytes predominating only in instances of secondary infection with pyogenic organisms. Liquefaction of the necrotic debris may occur, leading to cavity formation. Hyperemia, edema, interstitial inflammatory infiltration, bronchiolitis, proliferative and thromboangiitic vascular lesions are variable features. Interstitial, serous, fibrinous and proliferative pleuritis, alone or in combination, may occur.

The liver is generally somewhat enlarged, the average in our three cases being 1,950 grams. There is nothing remarkable in the gross appearance except the presence of multiple focal lesions that average 1 to 3 cm. in diameter. These spots are gray or yellowish in color and are less numerous in the liver than in the spleen. These lesions consist of coagulation necrosis of parenchyma with invasion of histiocytes, lymphocytes and occasional polynuclear leukocytes. In the remaining parenchyma there is evidence of toxic degenerative alteration.

The spleen is usually congested in cases dying during the first month; afterwards the enlargement is not found as frequently. Many foci not unlike those found in the liver are common in the early fatal cases. These foci tend to disappear after the first month in patients that live longer. Clumps of cells are numerous in the pulp, consisting of lymphocytes, plasma cells and polynuclear leukocytes. The caseous foci resemble those found in the liver. Reticuloendothelial hyperplasia is found in at least one third of the cases. The follicles are generally small and hypoplastic.

Case Reports

Case 1. G. M., a white male aged 43, was admitted to the York Hospital on November 17, 1938, with a temperature of 104° F. Five days previous to admission he had shot and cleaned two apparently healthy rabbits; three days later he had severe

chills and fever, nausea, intense headache, drenching sweats and marked diarrhea. He also noted pain in the region of the left thumb. On admission the man appeared desperately ill with high fever and rapid pulse, but the respirations were normal. The liver and spleen were not enlarged. The left thumb tip was tender with a brawny appearance. There was no lymphangitis but there was a nest of tender enlarged nodes in the left axilla; no other enlarged nodes were found. Blood studies were normal except a white cell count of 14,000 of which 58 per cent were segmented and 20 per cent were non-segmented neutrophiles; the remaining cells were lymphocytes. Repeated blood cultures remained negative and agglutination studies were normal. The patient appeared extremely intoxicated, he had repeated chills and sweats and a septic type of fever. He became irrational three days after admission. The lymph nodes in the axilla continued to enlarge and two days before death he developed a slight cough with signs of bronchopneumonia which was confirmed by roentgen study. The duration of his illness was 10 days. A few days after death the last blood culture revealed *Bacterium tularense*.

Postmortem examination was performed by Dr. Lewis C. Pusch, Pathologist to the York Hospital. The left axillary nodes were enlarged and contained caseous areas. The bulky areas of caseous necrotic cellular debris were bordered by histiocytes and lymphocytes. Each lung weighed 930 grams and was moist and dark red on gross section with a scattered distribution of grayish-brown areas of consolidation three to four cm. in diameter. Microscopically there were broad caseous masses of necrotic cellular debris bordered by alveoli filled with histiocytes and fewer leukocytes. The spleen showed many small mottled caseous foci identical in structure with those of the nodes and lung. The liver weighed 1910 gm. and showed an occasional focus similar in appearance to those described above. Smears of the exudate of the thumb, nodes and spleen revealed very small gram-negative organisms of bacillary and coccoid forms.

Case 2. E. E., a white housewife aged 52, was admitted to the York Hospital on November 13, 1939. On November 1, without using gloves she had cleaned several wild rabbits which her husband had shot and eviscerated. When handling the carcasses the husband had worn rubber gloves, but the patient had failed to observe this precaution. Five days later she noted malaise, slight fever, anorexia and severe headache. There was a bleb-like lesion on the right thumb which appeared with the onset of the disease and persisted throughout the course of the illness. The symptoms noted above gradually became more marked, and her temperature became septic in type. Physical examination revealed severe intoxication with a temperature of 103° F., pulse 118, and respirations 26 per minute. On the right thumb there was an ulcer 1.5 cm. in diameter with no lymphangitis, but in the right axilla there was a small nest of tender lymph nodes. Other than some distention of the abdomen and slight enlargement of the liver the findings were not remarkable. Initial laboratory studies revealed a small amount of albumin in the urine, mild hypochromic anemia with a leukocyte count of 7,600 with a normal differential count. Blood Kahn reaction was negative, as were all agglutination studies. Culture of the ulcer showed *Staphylococcus aureus*, and repeated blood cultures were sterile. The patient's course was rapidly downward and she lapsed into a stuporous condition. Repeated laboratory studies were essentially the same as on admission. She was treated with full doses of sulfonamides and repeated blood transfusions. She died 13 days after the onset of symptoms.

Postmortem examination by Dr. Pusch showed an enlarged right axillary lymph node, 2 cm. in diameter, which contained caseous foci. The node was markedly edematous and hyperemic with but little distinction between sinuses and medullary cords. The former were filled with lymphocytes, plasma cells, and macrophagic wandering cells, some of which contained phagocytized nuclear debris. The caseous

foci noted grossly consisted of areas of coagulative necrosis with karyorrhexis and little peripheral reaction. No areas of suppuration and very few polynuclear leukocytes were seen. The pericardial cavity contained about 50 c.c. of serosanguineous fluid; the heart and vessel were normal. About 450 c.c. of serosanguineous fluid were found in each pleural cavity. The pleural surface was covered with fibrin. The right lung weighed 590 gm., and the left one 510 gm. The bronchial tubes had grayish-red mucosae with gray coagulated exudate in the lumina. The tracheobronchial nodes were anthracotic. Cut surfaces of the lower lobes were moist, dark red and partly atelectatic. The upper lobes were moist and grayish-red. Several sharply circumscribed caseous white foci of irregular contour were found. Their diameters varied from 2 mm. to 2 cm. Although scattered throughout both lungs, they were seen chiefly in the lower lobes. The pulmonary capillaries were engorged with blood. Many alveoli were filled with plasma. The caseous white areas resembled those of the lymph node. Little or no phagocytized blood pigment was seen. The smallest and earliest lesions consisted of foci of lymphocytes and wandering cells with beginning karyorrhexis. The tracheobronchial lymph nodes were characteristic of tularemic lymphadenitis. About 200 c.c. of serosanguineous fluid were obtained from the peritoneal cavity. The gastrointestinal and biliary tracts, pancreas, and adrenal glands were not remarkable grossly, but the latter showed a marked toxic degenerative alteration, characterized by cytoplasmic swelling and vacuolation zona fasciculata of the cortex. The liver weighed 1,950 gm.; it was relatively homogeneous except for a scattered distribution of small white foci, 1 to 3 mm. in diameter. These foci resembled those in the lungs and nodes on histologic examination. The hepatic cells showed marked cytoplasmic swelling. The spleen weighed 690 gm. and presented scattered small solid white foci, 1 to 5 mm. in diameter; otherwise it was unremarkable. These focal necroses were not unlike those described above. The kidneys showed a toxic reaction with cytoplasmic swelling of the tubular epithelium. Bacteriology: Minute coccoid Gram-negative bacilli, in clumps, were present in smears of lesions in the axillary node and in the lungs, morphologically characteristic of *Bacterium tularense*.

Case 3. C. D., white male aged 35, was admitted to the York Hospital on November 19, 1938. During the first week in November he hunted rabbits and was successful on three different days. One week after the last hunting episode he developed a blister on a finger that healed spontaneously in a short time. About the same time he also developed what was thought to be an acute respiratory infection with chills, fever, sweats and general malaise. These generalized symptoms gradually increased in intensity, with severe headaches, and he was forced to stop work and go to bed. At no time was there any evidence of lymphangitis or lymphadenopathy. During the first week of the illness he noted a pain in the right chest, accentuated by deep breathing, reddish sputum and cough. The past medical and family history had no particular significance; the patient was a machinist by occupation. On admission he had a fever of 103° F., with normal pulse and respiratory rate. The only abnormal features were slight impairment of resonance and prolongation of the breath sounds in the upper half of the upper right lobe and slight enlargement of the liver. These lung changes were confirmed by roentgen studies of the chest which revealed an area of consolidation in that region. Blood count was normal except for 17,200 white blood cells, with a normal differential count. All agglutinations were normal except for *Bacterium tularense* which was positive 1:320. Blood Kahn reaction was negative. Sputum studies showed a large number of spirochetes and fusiform bacilli with many micrococci of the *Micrococcus catarrhalis* group; no acid-fast bacilli and very few pneumococci were found. Blood culture positive for *Bacterium tularense*. During the first week the patient ran a septic course with enlargement of the pulmonary consolidation on roentgen-ray examination and a drop in the leukocyte count to 7,500.

His clinical course was progressively downward in spite of repeated blood transfusions, sulfonamide medication in full therapeutic doses and other supportive treatment; during this period he showed extreme toxemia with a septic temperature, marked malaise and drenching sweats. During the fourth week in the hospital he developed marked edema of the right leg with large purpuric spots and right inguinal adenopathy. This was associated with distention of the abdomen and enlargement of the superficial abdominal veins. On the arms and abdomen ecchymotic spots appeared rapidly and became larger; at places they were confluent. No part of the body was free from this condition except the scalp. On a little finger a nodule appeared which rapidly ulcerated and from which a purulent discharge was cultured and revealed, along with a dense and varied bacterial flora, a Gram-negative bacillus compatible with *Bacterium tularense*. Ulceration developed over various parts of the body which yielded identical bacterial findings. During the course of the illness repeated blood cultures were positive for *Bacterium tularense*, and the agglutination test arose to a high titer. The roentgen and clinical studies of the lungs showed a progressive spread of the consolidation with cavitation to other parts of the chest. The patient died of toxemia on the seventieth day of the illness. In spite of three transfusions a week in which 60 donors were tested or used the blood count dropped progressively to a severe anemia, with hemoglobin 5 gm., red blood cells 1.2 million, and white blood cells 14,700, with 42 per cent segmented, 33 per cent non-segmented neutrophiles, 22 per cent small lymphocytes and 3 per cent monocytes.

Postmortem examination by Dr. Pusch: There were cutaneous ulcers of the right side of the face, back, ear, over the iliac crests, the little finger of the left hand, right leg and toes. The ulcers were in most part dry, and in part moist, foul, and sloughing. Some extended only into the subcutaneous fascia and others into muscle. The right pleural cavity was nearly obliterated by fibrous adhesions. The right lung weighed 1300 gm. All three lobes were ramified by irregularly shaped communicating zones of firm brownish-gray caseation from less than 1 to 3 cm. in diameter. Intervening pulmonary substance was firm and grayish-red but partly aerated. Irregularly shaped cavities from a few millimeters to 6 centimeters in diameter were scattered throughout the lung, the largest occurring in the lower lobe. Some contained a thick white exudate, others a rather thin reddish-gray exudate. The linings were in part soft and reddish-black, others were granular and gray with no appreciable wall except that of adjacent pulmonary substance, which in some places was caseated and in others grayish-red and partly aerated. Mediastinal nodes were anthracotic. The left lung weighed 840 gm. It was heavy, moist, predominantly red, not firm, with a cavity 8 cm. in diameter in the lower lobe, irregular in shape with a soft grayish-black lining and a wall of adjacent pulmonary substance. Microscopically the areas of consolidation consisted in part of broad areas of coagulation necrosis, in part of alveoli filled with polynuclear leukocytes, and in part of alveoli occupied by a network of fibrin enmeshing scattered leukocytes and histiocytes. Areas of consolidation were not homogeneous but included scattered aerated alveoli. The cavities were lined in part by tissue which had undergone coagulative necrosis, elsewhere by masses of polynuclear leukocytes. The linings generally were continuous, with similar structures in adjacent areas of consolidation, but in some areas a zone of epithelioid histiocytes intervened. Perivascular and intramural infiltrations of leukocytes and histiocytes in the walls of blood vessels were prominent features. Apparent lipin distention of the cytoplasm of many phagocytes was noticeable. Capillary engorgement was fairly generalized. In some areas, chiefly in atelectatic zones about cavities, proliferation of histiocytes lining the alveoli was conspicuous. The heart, large blood vessels and the anthracotic lymph node were unremarkable. The gastrointestinal and biliary tracts, kidneys, pancreas, and adrenal glands were unremarkable. Enlarged mesenteric nodes were found but were not abnormal on section. The liver weighed 1,750 gm., with

no visible necrotic foci; on section there were focal aggregations of histiocytes, lymphocytes and a few polynuclear leukocytes of variable localization resembling the focal hepatic lesions of typhoid fever; there was a moderate degree of toxic degenerative alteration. The spleen weighed 340 gm., with no visible focal lesions. On section there was reticuloendothelial hyperplasia. Sections of the adrenals showed cytoplasmic swelling of the cortical epithelium. Bacteriology: Smear of the white purulent exudate in the cavity in the upper lobe of the right lung showed staphylococci and an occasional intracellular group of minute Gram-negative coccoid bacilli.

Summary

1. The clinical details of tularemia have been considered, with a description of the rather common pulmonary complications.

2. The clinical features of the primary septicemia cases are compared with the average case of tularemia.

3. The laboratory diagnosis of the disease is described.

4. Pathologic studies of the lymph nodes, lungs, liver and spleen are considered.

5. Three case reports of autopsied cases are reviewed.

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THE DETECTION OF SUBCLINICAL SCURVY OR VITAMIN C DEFICIENCY *

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CLINICALLY classical scurvy is uncommon although cases are still encountered occasionally in infants and less frequently in adults. Is there a lesser degree of vitamin C deficiency which undermines health but is not manifest as scurvy? Nutrition is one factor over which we have some control. Optimal health is, of course, the goal of medicine and it assumes particular importance in times of national stress. If the vitamin C nutrition is suboptimal in any considerable portion of our population it is important that we should know it and define methods for its recognition.

Considered from a biochemical standpoint there is a wide variation in the nutritional status of various individuals relative to vitamin C. In any large series of cases, the concentration of ascorbic acid in the blood will be found to range from 0 to 1.3 mg. per cent. This latter value reflects a state of saturation. If vitamin C is administered to an individual so saturated the blood plasma concentration rises above this level and ascorbic acid is excreted in the urine. Although there is some variation, a plasma concentration of 1.3 mg. per cent represents the usual renal threshold.

Evidence is clear that the fasting plasma ascorbic acid level reflects the intake of vitamin C.[1, 2] Naturally if the plasma ascorbic acid value is found to be near the saturation level, vitamin C deficiency does not exist. If, on the other hand, the plasma ascorbic acid is low it does not necessarily indicate that the individual has suffered from the effects of vitamin C deficiency.

In this study we have undertaken to determine the degree of tissue depletion existing in cases with low plasma ascorbic acid values and whether or not this depletion has deleteriously affected the health of these individuals. Observations in this report deal only with adults.

Determination of the Vitamin C Deficit. The determination of the tissue reserves of vitamin C is relatively simple. If an individual with reasonable saturation of tissue is given a large test dose of ascorbic acid, the concentration of this substance in the blood plasma will rise, reaching a peak usually in two and a half or three hours, and a portion of the ascorbic acid will be excreted in the urine. If, on the other hand, the tissues are severely depleted there will be only a slight rise in the blood plasma ascorbic acid concentration and none will be excreted. Intermediate degrees of saturation

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give intermediate curves (figure 1). In this study we have used a standard test oral dose of 15 mg. of ascorbic acid per kilogram of body weight. After determination of the fasting plasma ascorbic acid level the test dose is given and the plasma concentration is again determined at three and five hours. The amount of ascorbic acid excreted in the urine during the five hour period is also determined. For the sake of simplicity the resulting blood plasma curves can be classified as flat (peak below 0.5 mg. per cent), medium (peak 0.5 to 0.9 mg. per cent), or high (peak above 0.9 mg. per cent) as shown in figure 1. Following this test the individual is given a known daily supple-

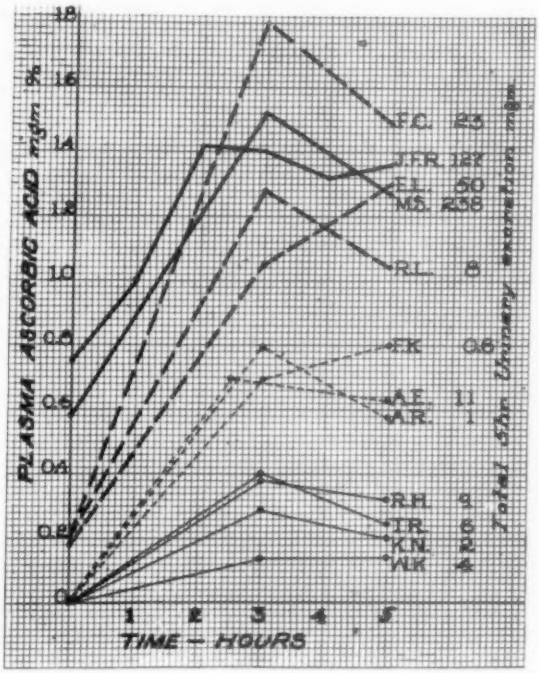

FIG. 1. Curves of plasma ascorbic acid concentration following test doses of 15 mg. per kilogram.

ment of ascorbic acid, and check determinations of the fasting plasma ascorbic acid concentration are made at intervals. When the fasting plasma level is at or near 1 mg. per cent saturation has been achieved and the degree of tissue depletion can be readily calculated. It has been found that the flat curves reflect marked tissue deficits. The tissue deficits ranged from 3 to 5 grams in 11 cases studied. All showed a deficit of 3 grams or more, with an average of 3.7 grams. This is the approximate degree of tissue depletion present in cases of clinical scurvy.[3] Of nine cases with medium rises all but one showed a deficit of 2 to 3 grams, with an average of 2.16 grams. Cases which exhibited a high curve without excretion are nearer saturation. In this group the average tissue deficit was 1.4 grams. Thus, it is seen that

the degree of tissue depletion can be determined with considerable accuracy by finding the three hour plasma concentration after administering a standard test dose of vitamin C.

The Significance of Low Plasma Ascorbic Acid Concentration. A comparison of the initial fasting plasma ascorbic acid concentration with the curves has been made to determine whether the fasting blood plasma level alone reflects the tissue depletion. This has been found to be so. Thus, of 34 cases with fasting plasma ascorbic acid values ranging from 0.0 to 0.1 mg. per cent, 15 showed flat curves representing an average deficit of 3.7 grams and 13 showed medium curves representing an average deficit 2.16 grams. The remaining six cases exhibited high curves. In only two instances was there any considerable excretion of ascorbic acid. Thus, 80 per cent of cases with fasting vitamin C values below 0.1 mg. per cent exhibited very considerable depletion of the vitamin C stores. A smaller number of cases with blood plasma ascorbic acid concentrations between 0.1 and 0.3 mg. per cent are available for similar analyses. Twelve of 19 cases with such fasting blood plasma levels showed medium three hour rises after the test dose of ascorbic acid. Others were high. These data are shown graphically in figure 2. With few exceptions, cases with initial blood plasma values above 0.3 mg. per cent were found to be near saturation and excreted from 50 to 300 mg. of the ingested dose of ascorbic acid.*

Determination of the tissue deficit is of interest but of greater practical importance is the evaluation of the significance of this deficit. At the outset it may be said that none of the cases included in this investigation showed the classical clinical picture of scurvy. Because of our special interest in the possible rôle of vitamin C deficiency in rheumatoid arthritis [5] many of the cases studied were suffering from this disease. Several others had other complaints. The objective clinical criteria for diagnosis of mild or subclinical scurvy are few. A moderately extensive and somewhat contradictory literature revolves around the significance of capillary resistance tests. So

* These values represent the true concentration after subtraction of the ascorbic acid equivalency of the dye used in developing the end point in a blank. Naturally it is necessary that the titration be done carefully by an experienced technician with avoidance of the various factors that might give false values. We have used a modification of the original Farmer and Abt [4] method as follows: 5 to 6 c.c. of fasting blood are collected in a test tube containing dry powdered sodium oxalate. The blood is centrifuged, and 2 c.c. of the clear plasma are placed in a centrifuge tube. To it are added 4 c.c. of distilled water and 2 c.c. of 5 per cent sodium tungstate followed by 2 c.c. of N/3 sulfuric acid. After thorough mixing the tube is allowed to stand for one to two minutes, then centrifuged. Two cubic centimeter portions of the supernatant fluid are pipetted into conical shaped centrifuge tubes and titrated with a dilute dye solution to the first faint pink color which remains for approximately 30 seconds. A microburette graduated in 0.01 or 0.02 c.c. is used for measuring the dye solution.

A stock dye solution is prepared by dissolving 50 mg. of 2,6 dichlorophenolindophenol in 100 c.c. of hot water, cooling, restoring the volume to 100 c.c., and filtering. If a pinch of sodium bicarbonate is added it improves the keeping quality of the dye solution. The stock dye solution is kept in the refrigerator and is good for about three weeks. It is standardized frequently against pure crystalline ascorbic acid. The stock dye is usually found to have an ascorbic acid equivalency of 0.2 to 0.25 mg. per c.c. To prepare the dilute dye for use in titration, one volume of the stock dye is diluted accurately with 19 volumes of water to give a dilution of 1/20. The resulting dye solution will have a value in terms of A.A. of 0.01 to 0.0125 mg. per c.c.

many factors may contribute to a lowered capillary strength that taken alone the test is of little value in detection of subclinical scurvy. It is not the purpose of this paper to review this controversy. There is, however, general agreement that although the capillary strength is reduced in many other conditions than vitamin C deficiency it is usually, though not invariably, also reduced in this condition. If a clearly reduced capillary strength can be ele-

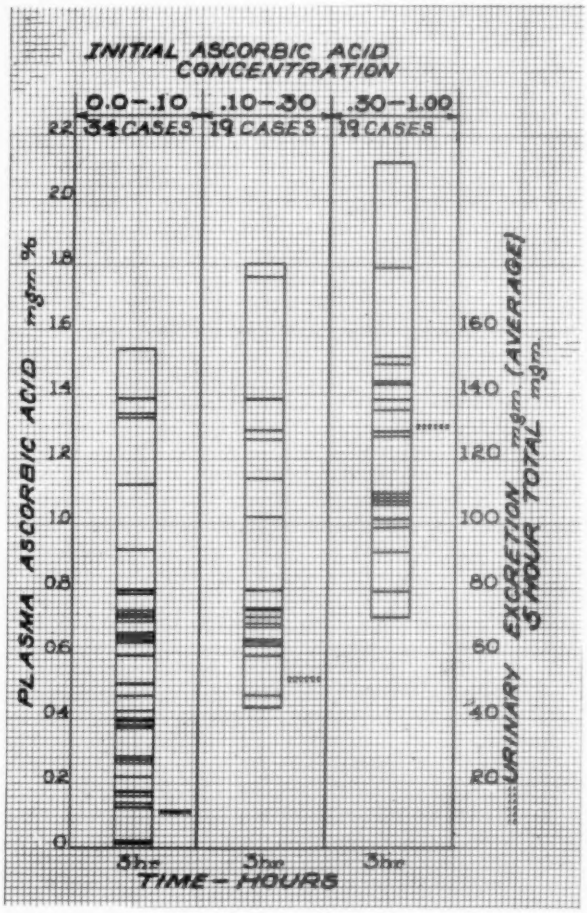

FIG. 2. Showing two and a half to three hour level of plasma ascorbic acid after test doses of ascorbic acid of 15 mg. per kilogram. Each cross bar represents the peak level of an individual case in the concentration range indicated.

vated by the simple administration of vitamin C, it may be considered valid evidence that vitamin C deficiency was the basis of the reduced capillary strength.

In determination of the capillary resistance we have used the instrument of Dalldorf [6] in which controlled suction tension is applied to the skin through a standard glass cup. Because the capillary strength varies in dif-

ferent skin areas, it is essential that the same skin area be used in making comparative tests. In this study we have used the outer aspect of the upper arm (vaccination area). The skin surface is thinly smeared with vaseline and inspected under good light for preëxisting petechiae or confusing marks by pressing a glass slide against the area to be tested. The glass cup is then applied to this area; the desired suction tension is made and maintained by closing the valve leading from the pump. The suction is applied for a standard interval of one minute and then released by opening the valve. The area beneath the cup is again inspected for the presence of petechiae through a glass slide pressed against the skin and the number of petechiae is counted. The capillary strength then can be expressed in terms of the negative tension and the number of petechiae resulting, thus — 20/10 would indicate that 10 petechiae resulted from a negative tension of 20 cm. of mercury applied for one minute.

As in most subclinical deficiency states the effect on the general health and well-being of the patient following correction of the deficiency is perhaps the clearest evidence that deficiency existed.

On analysis of this series of cases in which five hour blood studies have been made, it is clear that a high percentage of those with fasting ascorbic acid concentration below 0.1 mg. per cent were suffering from the effects of inadequate vitamin C intake even though none of the cases presented a clinical picture that would be classified as scurvy by the usual criteria. Of 27 cases studied, 19 showed a lowered capillary strength. Thirteen of 16 cases which were followed after administration of vitamin C showed an elevation of the capillary strength. This elevation was apparent usually within two weeks. Seventeen of 22 cases followed after administration of vitamin C showed definite clinical improvement. Increased energy, loss of fatigability, and improved appetite were prominent clinical effects. As previously noted, many of the persons studied had rheumatoid arthritis. Improvement of the arthritis in varying degrees was noted in many cases. These observations will be reported subsequently in greater detail in a large series of cases. Reticulocyte counts were made in 10 of the cases. In seven there was a definite though mild reticulocytic rise following administration of vitamin C. This occurred even though the anemia present may have been mild. Twenty-three of 27 cases with initial plasma vitamin C concentration below 0.1 mg. per cent showed one or more of the effects noted after correction of the vitamin C deficiency. It is evident from this analysis that approximately 80 per cent of the cases in this series in which the initial fasting blood plasma ascorbic acid was below 0.1 mg. per cent were suffering from a subclinical form of vitamin C deficiency.

Observations on cases with fasting plasma ascorbic acid concentrations ranging between 0.1 and 0.3 mg. per cent are too few to be conclusive although it is clear that many had considerable tissue deficits and at least some of this group were suffering from effects of vitamin C deficiency. Several individuals in this group were known to have been taking fair amounts of

vitamin C, and it is probable that they had some fault in absorption of the vitamin. The cases in which the fasting plasma ascorbic acid concentration was above 0.3 mg. per cent showed little tissue depletion, and it seems unlikely that they suffered significant deficiency.

The cases abstracted below illustrate the observations upon which this study is based.

A. R., female, aged 23, complained of mild gingivo-stomatitis with small pharyngeal ulcers which bled. Initial plasma ascorbic acid was 0.02 mg. per cent. Curve following test dose of ascorbic acid (15 mg./kilo) showed a medium rise to 0.78 mg. per cent. No excretion. Deficit approximately 2 grams. Initial capillary resistance — 20/40. Elevation of capillary resistance to — 20/12 in three days. Slight reticulocyte rise. Healing of pharyngeal ulcers.

W. K., male, aged 57. Diagnosis: Mild rheumatoid arthritis with slight swelling and stiffness of metacarpophalangeal and interphalangeal joints and soreness in knees and shoulders. Initial plasma ascorbic acid 0.0. Curve following test dose of ascorbic acid very flat, three hour peak, 0.13 mg. per cent. Deficit 3 grams. Initial capillary resistance — 15/90. Elevated to — 16/8 in six days. Very mild reticulocyte response. Two months later general health and arthritis greatly improved.

T. R., male, aged 33, complained of paresthesia of both hands in ulnar nerve distribution. Fasting plasma ascorbic acid 0.0. Curve following test dose of ascorbic acid flat. Three hour peak, 0.4 mg. per cent. Deficit 3 grams. Initial capillary resistance — 20/50. Increased to — 20/12 ten days after administration of ascorbic acid. Paresthesias relieved.

M. M., male, aged 31. Diagnosis: Rheumatoid arthritis of the spine. Initial plasma ascorbic acid level 0.0 mg. per cent. Curve following test dose of ascorbic acid very flat. Three hour level 0.17 mg. per cent. Deficit 4 grams. Questionable slight rise in capillary resistance from — 16/4 to — 20/1 after 21 days. No reticulocyte studies. Improvement in general health; sleeps better, less back pain.

W. H., male, aged 38. Diagnosis: Rheumatoid arthritis of the spine. Initial plasma ascorbic acid 0.0 mg. per cent. Curve following test dose of ascorbic acid (15 mg./kilo) medium rise to peak of 0.6 mg. per cent. Tissue deficit 2 to 3 grams. Capillary resistance rose from — 15/6 to — 20/6 in 60 days. Increased energy and appetite. Less pain and increased movement in spine. Clear cut slowing of sedimentation rate.

E. L., female, aged 30. Diagnosis: Mild rheumatoid type of arthritis. Initial plasma ascorbic acid 0.28 mg. per cent. Curve medium rise to 0.68 mg. per cent. Five hour level higher. No excretion. Second curve three hour level 1.28 mg. per cent. No excretion. Deficit 2.5 grams. Capillary resistance normal. No reticulocyte rise. Marked symptomatic improvement in general health and arthritis. Diet history good. Probable absorptive fault.

Incidence of Subclinical Scurvy. We have seen that in the adult the severely lowered plasma ascorbic acid levels afford strong presumptive evidence of clinically significant vitamin C deficiency.

An analysis of data concerned with blood plasma values in 'health' and disease will be the subject of a subsequent report. It may be said, however, that vitamin C deficiency of the type described is frequently encountered. In a group of 239 'normals' consisting of students, nurses, house officers and laboratory workers 4.6 per cent showed fasting blood plasma levels below 0.1 mg. per cent and 16 per cent were below 0.3 mg. per cent. In

various diseases we have found the incidence of vitamin C depletion much higher. These findings correspond to the observations of Wright [7] that clinically significant vitamin C deficiency is common.

Discussion

The daily requirement for vitamin C has not been established with certainty. Ralli, Friedman and Sherry [8] have shown that the adult requires approximately 100 mg. per day to maintain the blood in a state of saturation, i.e., at or above 1 mg. per cent. Whether or not a lesser amount of ascorbic acid suffices for normal metabolism has not been established. The observations of Ralli et al. suggest, however, that a plasma ascorbic acid level in the vicinity of 0.5 mg. per cent may be maintained with an intake of 50 to 75 mg. a day. We have shown that tissue depletion of persons with blood concentrations in this range is minimal. It would appear unwise at present to consider plasma concentrations above 0.3 mg. per cent (0.3 to 0.8 mg. per cent) as indicating deficiency even though they do not reflect saturation.

The experiments of prolonged acute vitamin C deprivation in man are of interest but must be properly evaluated. Schick [9] deprived himself of vitamin C containing foods for a period of 160 days without showing any clear-cut evidence of vitamin C deficiency. Crandon [3] subjected himself to vitamin C deficiency for six months and except for fatigability at three months and gradual weight loss, no evidence of deficiency was manifest during the first four months. At 132 days hyperkeratotic skin papules appeared, and perifollicular hemorrhages were first evident in 161 days. It is of interest that the tissue deficit in each case was approximately 4 grams. This probably represents the approximate total vitamin C stores in the human adult. In the Crandon experiment, it should be remembered that all other vitamins were supplied in excess and that the vitamin C stores were good at the outset of the experiment and presumably had been so in the past. In clinical medicine very different circumstances prevail. From analysis of dietary histories, evidence is clear that many of the subjects of this study had been taking minimal amounts of vitamin C for years. Absolute lack of vitamin C is uncommon, but it appears that practically complete deprivation of ascorbic acid is necessary for the development of the picture which we recognize as classical clinical scurvy. On the other hand, long standing suboptimal intake is much more common. It is probably the chronic deficiency that we have recognized in the study. The designation of chronic scurvy might be more appropriate than the term subclinical.

Observations of Kramer [10] and Roff and Glazebrook [11] are worthy of note. Kramer studied 34 soldiers in the German air force who were suffering with gingivitis and stomatitis. He found the average ascorbic acid tissue deficit to be 2 to 2.5 grams, and treatment with ascorbic acid effected a cure in each case except one. In addition to the local oral pathologic lesions fatigue, leg pain and anorexia were very prominent symptoms which

were also relieved by administration of vitamin C. This is in accord with our own observations. Roff and Glazebrook described cases of gingivo-stomatitis among boys in a training establishment of the Royal Navy. The gums were congested and spongy, the surfaces having a gelatinous feel. Bleeding did not occur on simple palpation, but if one pierced with a probe the hemorrhage was more copious than usual. The congestion was uniform, from the gums into the sulci on to the buccal mucous membrane, extending backwards and involving the tonsils and pharyngeal wall as far as the eye could see. In all cases vitamin C deficiency was found with an average ascorbic acid deficit of approximately 4 grams. The condition responded to administration of ascorbic acid. These authors also recorded prominent symptoms of lassitude and rheumatic pain in and around the larger joints. They note that exactly similar symptoms occur in cases in which there is evidence of infection, and that such cases may later develop rheumatic fever, with true arthritis; or carditis may develop silently without further manifestations of rheumatism. They note: "It is often impossible to differentiate from the description of the symptoms of the patient a case which will clear up on saturation with vitamin C, from one which will tend to progress to rheumatism and carditis." They further found that the highest incidence of scorbutic gingivo-stomatitis and of rheumatic fever fell upon recruits from a given area in which the economic conditions were below standard for the country as a whole.

Various hemorrhagic manifestations may be encountered in vitamin C deficiency. In cases of unexplained purpura or other bleeding, vitamin C deficiency should be considered as a possible major or contributory factor. Although many cases will be found to be dependent upon other factors a determination of the fasting plasma ascorbic acid is indicated in such cases.

Summary

Determination of the fasting plasma ascorbic acid is the simplest, most direct exploratory method in detection of subclinical vitamin C deficiency or scurvy. A simple method for determination of the degree of tissue depletion is presented. This is based upon the rise in the plasma ascorbic acid following a standard peroral test dose of ascorbic acid (15 mg./kg.). Flat curves reflect severe tissue depletion, medium curves, moderate depletion. Eighty per cent of cases with fasting blood plasma levels below 0.1 mg. per cent showed marked or moderate tissue deficits of ascorbic acid which ranged from 2 to 5 grams. In approximately 80 per cent of cases with fasting plasma ascorbic acid levels below 0.1 mg. per cent, demonstrable improvement followed administration of vitamin C. Thus, concentrations in this range afford strong presumptive evidence of subclinical scurvy. Fasting plasma vitamin C values between 0.1 and 0.3 mg. per cent are probably indicative of significant deficiency in a smaller percentage of cases, but data in the group are not adequate for judgment. Cases with plasma ascorbic acid

levels ranging from 0.3 to 0.8 mg. per cent show only mild tissue depletion, and it appears unlikely that they are suffering from vitamin C deficiency even though the tissues are not saturated.

Objective criteria for detection of vitamin C deficiency are few. A lowered capillary strength per se is of little value as an index of such deficiency. However, a lowered capillary strength that is elevated by administration of ascorbic acid is acceptable evidence of preëxisting vitamin C deficiency. Mild reticulocyte responses following administration of vitamin C may prove a useful objective index of deficiency. This should be studied further. General symptoms of lassitude, fatigability, anorexia and rheumatic pains are frequent in the presence of vitamin C deficiency. Gingivitis and gingivo-stomatitis occur commonly enough to arouse the suspicion of hypovitaminosis C. Vitamin C deficiency should be considered as a major or contributory factor in cases of unexplained bleeding. Unpublished observations indicate that vitamin C deficiency or subclinical scurvy of the type described is commonly encountered in medical practice.

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CORONARY OCCLUSION; A CLINICAL STUDY OF 100 PATIENTS *

By Carter Smith, M.D., F.A.C.P., H. Cliff Sauls, M.D., F.A.C.P., and James Ballew, M.D., *Atlanta, Georgia*

As the diagnosis of coronary occlusion has become more and more precise, many clinical and pathological studies of patients with this disease have been added to the literature. Master, Dack and Jaffe[1] have recently reported a study of 500 patients with coronary occlusion seen at the Mount Sinai Hospital and have adequately reviewed the entire literature on this subject. Their bibliography includes the clinical reports of 2,803 patients with this disease and necropsy studies in 1,241 other patients with coronary occlusion. This recent complete review obviates the necessity for another detailed survey of the literature.

Material

Since 1930, 100 private patients with coronary occlusion have been studied by us. Seventeen of the series were referred by other physicians, and their clinical courses were followed through the referring physician.

Table I

Sex, Age Incidence and Subsequent Clinical Course

In 100 Patients
Male 85
Female 15

Well	Sick	Dead
54	12	34

Clinical Course of Different Age Groups in Decades

Youngest patient 28 years of age
Oldest patient 78 years of age

Decade	20–30	30–40	40–50	50–60	60–70	70–80	Total
Living	0	3	17	30	10	6	66
Dead	1	1	7	10	13	2	34

Mortality Rates

Immediate mortality (within 21 days)	12
Subsequent mortality	22
Total mortality	34

Sex, Age, Incidence, and Subsequent Clinical Course (Table 1). Fifteen patients in our series of 100 were females. This is a ratio of 6.6: 1, and was considerably lower than the 3: 1 ratio of the entire literature. The ratio range in all clinical cases reported in the literature was between 3: 1

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and 13 : 1. This, then, is a reasonable average when compared with those previously reported.

Age Distribution (Table 1). This did not vary materially in our series from those previously reported. Our youngest patient was 28 years old, and the oldest was 78 years old. Five per cent of our patients were less than 40 years of age. In the series of Master et al.,[1] 7.8 per cent were below 40. Except for a slightly greater number of patients occurring in the sixth decade, our age distribution was quite similar to previously reported studies. Peak incidence was definitely shown to belong to the sixth decade, 40 per cent of the patients falling in this age level.

Mortality Rate (Table 1). There was an immediate (within 21 days) mortality of 12 per cent and a total (immediate and subsequent) mortality of 34 per cent in this series. Sixteen patients died in subsequent attacks of coronary occlusion, four died of subsequent congestive heart failure, and two died of causes unrelated to cardiac disease. The mortality rates of different decades remained practically constant except in those between the ages of 60 and 70. Here was found more than a 20 per cent increase in the average 34 per cent mortality for the group. From previously reported studies the mortality rate of patients in the second and third decades was definitely less than in the older groups. This was not apparent in our series, and was probably due to the small number of patients in this age group. Our mortality rate in women was two out of 15 (13.3 per cent). This was much less than the average mortality rate for the entire group and differs from the majority of studies reported by other workers.[2, 3, 4] The higher mortality in women has been attributed to the greater incidence of diabetes. In our series only two of the 15 women were diabetics and both of these patients are living and well.

TABLE II

Length of Observation

In 66 Patients Who Recovered from Coronary Occlusion

3 years or less	36
3 to 6 years	17
6 to 9 years	12
Over 9 years (23 years)	1

Length of Observation (Table 2). In 66 patients who have survived the initial attack of coronary occlusion, 36 have been followed three years or less, 17 were studied from three to six years, and 12 were studied from six to nine years. The oldest individual in the group has been followed by one of us for 23 years. He is now living and well.

Length of Life After the Initial Attack in 34 Patients with Fatal Coronary Occlusion (Table 3). Of this group, 13 died in less than 21 days after the initial attack, 10 others died within 10 months after the initial attack, and of the remaining 11, 10 died within 28 months after the initial

TABLE III

Length of Life After Attack
In 34 Patients With Fatal Coronary Occlusion

Less than 24 hours	4
Less than 7 days	5
Less than 14 days	1
Less than 21 days	3
Less than 28 days	2
Less than 2 months	4
Less than 3 months	4
Less than 5 months	1
Less than 9 months	1
Less than 20 months	3
Less than 28 months	5
6 years and 2 months	1

attack. One patient lived six years and two months, only to die of chronic congestive heart failure.

Recurrent Coronary Occlusion and the Time After the Initial Attack (Table 4). Twenty-five per cent of the patients in this study had recurrent

TABLE IV

Recurrent Coronary Thrombosis and Time After Initial Attacks
100 Patients

Fatal 2nd Attack 15 Patients	Fatal 3rd Attack 1 Patient	Non-fatal 2nd Attack 5 Patients	Non-fatal 3rd Attack 4 Patients
6 days	6 years, 2 months	2 months	9 months
7 days		3 months	10 months
14 days		4 months	18 months
17 days		17 months	18 months
21 days		38 months	
4 weeks			
6 weeks			
7 weeks			
3 months			
3 months			
5 months			
5 months			
1 year			
1 year			
2 years, 6 months			

attacks of coronary thrombosis. In all but three patients the recurrent attacks came within two years after the initial attack. Fifteen of the 25 patients died in the subsequent attacks. This mortality rate of 60 per cent is almost double that of the initial attacks (34 per cent).

Occupation and Race (Table 5). As has been previously demonstrated,[5] coronary occlusion occurs more often in the higher orders of intellect of the Caucasian race. Those engaged in professional occupations or positions of responsibility are most often victims of the disease. In this series, 67 per cent were business men of the executive type, or those engaged in small businesses requiring much individual effort and initiative. The frequent occurrence among traveling men is of interest. This suggests the vulnerability of those who work hard and participate in irregular living and habit

TABLE V

Occupation and Race

In 100 Patients With Coronary Occlusion

Business men	30
Business executives	23
Traveling salesman	14
Physicians	10
Lawyers	4
Interior decorator	2
Night watchman	2
R. R. engineer	1
Farmer	1

Race Distribution

All White

Gentile	Hebrew
90	10

excesses. Ten per cent of the patients in this group were physicians. This probably represents the highest "occupational per cent" found in the series.

Habit Excesses (Table 6). An attempt was made to evaluate habit excesses that might in some way be responsible for the development of this

TABLE VI

Habit Excesses

In 100 Patients With Coronary Occlusion

Eating	32
Smoking (12 did not smoke at all)	17
Liquor	11
Worry	25
Work	41
No bad habits	3
Data insufficient	22

disease. Excess work, largely mental, was found in 41 per cent and was the most common over-indulgence. Over-eating came next and was found in 32 per cent. Excess worry came third, being found in 25 per cent. Nicotine played an inconclusive part. Seventeen per cent over-smoked, but 12 per cent did not use tobacco at all. Liquor, as has been shown before,[6] plays little if any part in the production of coronary occlusion. Eleven of the group were excessive drinkers, but in no instance did the attack occur during an alcoholic bout. In many patients, whiskey was used to advantage in controlling attacks of anginal pain.

The combination of over-eating, over-working, and excess worry seems to form the most potent combination of the etiologic factors.

Diseases (Other Than Vascular) Associated with Coronary Occlusion (Table 7). In 51 of these patients no disease other than that of the vascular tree was found. As evidence of the previously discussed excess eating habit, obesity was common and occurred in 35 of the 100 patients. Malnutrition was quite uncommon and occurred in only 4 per cent of the group.

TABLE VII

Diseases Associated With Coronary Occlusion
In 100 Patients

Obesity	35
Malnutrition	4
Diabetes mellitus	8
Chronic cholecystitis	9
Abscessed teeth or tonsils	3
Chronic bronchitis	9
None detected	38

Diabetes mellitus was found eight times, this frequency being slightly less than that described in other studies. Master et al.[1] found 11.2 per cent in their series of 500 patients (mostly Jewish). Conner and Holt[7] found about 11 per cent diabetics in a series drawn largely from gentiles. All but one of our diabetics was more than 50 years of age, and none was less than 45 years of age. The sexes were equally divided in the diabetics of the series. In those reported in the literature,[1] diabetes was four times more frequent in women.

Chronic cholecystitis was found nine times in the 100 patients. In one patient, coronary occlusion followed cholecystectomy. In four patients oral infections (abscessed teeth or tonsils) seemed closely associated with the acute onset of coronary thrombosis. Removal of abscessed teeth was followed by coronary occlusion in three patients. Only two patients in the entire group had the acute attacks of coronary occlusion precipitated by operation—one cholecystectomy and one prostatectomy. In a previously reported study[8] 5.6 per cent of 625 patients with coronary occlusion developed the attack after major surgical procedures. In three patients with chronic bronchitis, coughing paroxysms may have been associated with the acute coronary thrombosis.

TABLE VIII

Events Associated With Immediate Attacks
In 100 Patients With Coronary Occlusion

Physical exertion	32
While in bed	10
During or immediately after a meal	5
Severe emotional upset	4
Major surgery (prostatectomy-cholecystectomy)	2
Insufficient data	47

Events Associated with the Immediate Attack (Table 8). In 49 patients no significant event could be associated with the immediate attack. In 32 of the remaining 51 patients physical exertion of varying degrees was associated with the onset of the acute attack. Ten patients, however, had the acute attack while in bed. This may have been associated with a slowed blood flow occasioned by bed rest. In five patients coronary occlusion occurred after a large meal. A severe emotional upset seemed to precipitate the attack in four patients.

From an analysis of the events associated with the immediate attack, it seems that an increased circulatory load is the precipitating factor in the majority of the patients, but in 19.6 per cent (10 of 51) the acute coronary closure occurred in a resting state and was probably associated with a slowed blood flow.

TABLE IX

Complications Associated With Immediate Attack
In 100 Patients With Coronary Occlusion

Circulatory collapse	31
Cerebral embolism	5
Pulmonary embolism	3
Popliteal embolism	2
Renal suppression (fatal)	1
Psychosis	3
Pleural effusion	2
None	53

Complications Associated with the Immediate Attack (Table 9). Circulatory collapse complicated the immediate attack in 31 patients. This was a grave prognostic sign, and 21 of these 31 patients died.

Embolic phenomena occurred in 10 per cent of our patients. In a previously reported study[9] embolic phenomena were found in 14 per cent of all patients with cardiac infarction. Occasionally embolic phenomena occur as the only symptom of a recent coronary occlusion. History and electrocardiogram will usually reveal the occurrence of the cardiac infarction which has been responsible for the embolus.

Psychoses that were transient occurred in 3 per cent of the series.

Fatal renal suppression following circulatory collapse was encountered once.

In 53 of the 100 patients, no complications were associated with the immediate attack. The mortality rate in this group was considerably lower than that for the entire group.

The Occurrence of Angina Pectoris Before and After Coronary Occlusion (Table 10). Thirty-three patients of the group had angina pectoris

TABLE X

Angina Pectoris
Before and After Coronary Occlusion in 100 Patients

Previous and subsequent angina	33
No previous but subsequent angina	23
Previous but no subsequent angina	13
No angina before or after coronary occlusion	15
Indefinite history as to previous or subsequent angina	6
Previous angina in 12 who died in the immediate attack	10

both before and after coronary occlusion occurred. In many instances, however, the degree of angina was less after the attack of coronary occlusion. Twenty-three patients denied having angina previous to the attack of coronary occlusion, but complained of it as a post-occlusion symptom. In

13 patients angina disappeared after coronary occlusion occurred. Fifteen patients denied cardiac pain either before or after the acute attack. It was possible, however, to get from some in this group symptoms of palpitation, shortness of breath, and substernal oppression.

TABLE XI

Referred Pain and Abdominal Distress
In 100 Patients With Coronary Occlusion

Epigastrium	14
Elbows or arms	22
Shoulders	4
Cervical vertebrae	2
Lumbar vertebrae	1
None (all pain substernal or precordial)	23
Data insufficient	34
Abdominal distress	50

Referred Pain and Abdominal Distress (Table 11). Many observers have pointed out the areas to which coronary pain may be referred. A knowledge of these is important to a correct differential diagnosis. Herrick,[10] in 1935, listed 28 different diseases that were diagnosed as coronary occlusion. These 28 diseases illustrated practically all points of referred pain.

An analysis of the referred pain in 46 patients of the group shows it to have occurred in practically all points that have previously been described. The epigastrium and upper extremities were the most frequent sites of pain refer. In 23 patients no history of any referred pain could be elicited. Abdominal fullness and epigastric distress occurred in slightly more than half of the patients, and was in some the most difficult of all symptoms to control.

Blood Pressure Studies Before and After Coronary Occlusion (Table 12). In previous studies hypertension has been found in 33 to 73 per cent of patients as an antecedent to coronary occlusion. Levine's series [11] showed

TABLE XII

Blood Pressure Studies Before and After Coronary Occlusion
In 100 Patients

Before Attack		After Attack	
High	to	High	18
High	to	Normal	7
High	to	Low	16
Normal	to	High	2
Normal	to	Normal	27
Normal	to	Low	19
Low	to	High	0
Low	to	Normal	0
Low	to	Low	9
Insufficient data			2

Summary of Blood Pressure Findings

Before Attack			After Attack		
High	Normal	Low	High	Normal	Low
41	48	9	20	34	44

40 per cent hypertensive. In the series by Master et al.,[1] 62.4 per cent of their patients had an antecedent hypertension. They thought that even this figure was lower than the actual incidence. In our series 41 of the 100 patients were known to have had a previously existing hypertension. Hypertension persisted in only 18 patients after coronary occlusion. Normal or low blood pressure after the attack of coronary occlusion was found in 78 per cent. This reduction in pressure persisted in many for months, or even years, following the coronary occlusion.

Of the 59 patients with normal or low blood pressures antedating the coronary occlusion, only two were abnormally high after the attack.

In this study there was no demonstrable connection between mortality rate and previously existing hypertension. The incidence of hypertension in women with coronary occlusion has been shown to be[1] 32 per cent higher than that found in men. This finding was corroborated in our series.

TABLE XIII

Cardiac Hypertrophy and Degree of Arteriosclerosis
In 100 Patients With Coronary Occlusion

Cardiac Hypertrophy (found in 59 patients)				
None Found	One Plus	Two Plus	Three Plus	Four Plus
41	19	31	8	1
Arteriosclerosis (found in 97 patients)				
None Found	One Plus	Two Plus	Three Plus	Four Plus
3	33	43	20	1

Cardiac Hypertrophy (Table 13). Enlargement of the heart was found in 59 per cent of our patients. Progressive cardiac hypertrophy was observed in 10 per cent of the patients following cardiac infarction. In this series the relation of hypertrophy and hypertension was not clear, but there was a very definite parallel between cardiac hypertrophy and mortality rate. Both immediate and subsequent mortality was materially increased in those with cardiac hypertrophy.

Arteriosclerosis: Some degree of arteriosclerosis could be demonstrated in 79 per cent of our patients. In the majority (76 per cent) it was not marked in the large palpable vessels. There was little demonstrable relationship between the degree of peripheral arteriosclerosis and the mortality of coronary occlusion. This would indicate that the degree of arteriosclerosis or atherosclerosis present in the coronary arteries could not be determined from that manifested in peripheral vessels.

COMMENT

After studying this group of patients and those of other workers, we are left with an attempt to answer such questions as these. Why do certain

individuals have coronary occlusion whereas others with even more evident vascular pathology do not? Why do certain patients recover from the attack and others either die immediately or of subsequent cardiac failure? Why will some die suddenly without history of previous coronary insufficiency and with a normal electrocardiogram? What habit excesses in our modern method of living are responsible for the apparent increase in the disease? In one that is a coronary suspect, what things should be done or avoided in order to prevent the development of an acute coronary closure? And last, but of considerable importance, what is best to do for a patient after coronary thrombosis has developed?

Complete answers to these questions are not yet available, but our increasing knowledge from continued study does throw light on some. That the disease is more prevalent in the higher orders of intelligence is evident. Those occupying positions of responsibility are most often victims. The colored race, even though quite emotional, have very little of the disease. It has been found in only 14 patients (.63 per cent) of 2,204 cardiac patients of all types studied at the Colored Grady Hospital during the past 10 years. This low incidence is further substantiated by postmortem examinations. In the White Grady Hospital coronary occlusion occurred in 3.4 per cent (17 of 496 patients in 1938) of all cardiac patients. In this series of private office and hospital patients the frequency of coronary thrombosis compared to all other types of heart disease was approximately 10 per cent. The prevalence of hypertension and arteriosclerotic disease in the colored race is well known and undoubtedly exceeds that found in the white race, especially in the third and fourth decades. Yet they are almost immune from coronary occlusion. This leads one to the conclusion that the added factor of a high-tensioned sympathetic nervous system and an exaggerated sense of responsibility are a combination that in some way produce the disease regardless of the degree of generalized vascular disease and hypertension that exists.

A consideration of why some patients die of coronary thrombosis whereas others recover seems to revolve principally around the rate of speed with which the coronary occlusion occurs, and the degree of underlying coronary artery and myocardial disease that is already present at the time of the acute closure. Those who have a minimal amount of co-existing myocardial and coronary disease and who occlude gradually so that time is allowed for the establishment of a collateral circulation apparently have the best prognosis, both as to mortality and morbidity. Those who have considerable preëxisting myocardial and coronary disease and who experience rapid closure of the coronary artery stand less chance of recovery.

Early diagnoses and proper treatment of the immediate attack should materially reduce morbidity and mortality rates. In a patient with suspected coronary occlusion, absolute bed rest should be maintained until the true diagnosis is established. Two or more electrocardiograms should be

made during this period of observation. Often an interval of five to seven days is necessary before the electrocardiogram will confirm or disprove the suspected diagnosis. Occasionally, longer periods of observation are necessary. In this series one patient did not show positive electrocardiographic changes until 15 days had elapsed, and in another characteristic changes were not found until the fifth week. The finding of a leukocytosis and an increased sedimentation rate often help in establishing a correct diagnosis.

Treatment

After a definite diagnosis is established the following treatment should be carried out.

Complete bed rest should be strictly enforced during the critical 21 day post-occlusion period. Modifications as to the amount of bed activity during this time would be determined by the severity of the attack. For the milder attack four to six weeks of bed rest should be enforced. For the more severe attacks eight to 10 weeks of complete bed rest are necessary. Convalescence should be gradual and should be systematically planned.

Relief of pain is of paramount importance. Opiates will be necessary in the more severe attacks. Extreme caution should be exercised in the effort to prevent nausea and vomiting from opiates. This complication alone may precipitate a fatal ventricular rupture, ventricular fibrillation, or embolus formation.

The combined use of opiates with sodium luminal, aminophyllin by vein or rectal administration, and oxygen inhalations will often relieve pain without producing nausea, and less opiate is required than if opiates alone are used. Small doses of whiskey have a vasodilating and pain relieving effect. Diathermy over the precordium is of questionable value in relieving residual anginal pain after healing has occurred. Diathermy should not be used during the healing period.

The relief of dyspnea is most satisfactorily effected by continuous oxygen inhalations. Rectal or intravenous injection of aminophyllin will often give great relief from the orthopnea and dyspnea of acute left ventricular failure.

The care of the gastrointestinal tract is important. Gaseous distention should be prevented by small frequent feedings of liquid and soft diet. Dextrose given in water at two hour intervals is helpful. Occasionally, it will be necessary to give fluids and dextrose by hypodermoclysis. Fluids should never be given by venoclysis.

Small doses of laxatives given frequently will often help prevent abdominal distention. Heat applied to the abdomen is of value. Prostigmin or pitressin should not be used to combat flatulence.

Small enema of oil and glycerin (six to eight ounces) should be used exclusively rather than the usual 2 liter enema of saline. The larger enemas may, by their exhausting effect and the increased abdominal pressure, produce a fatal complication.

Cardiac Medication: Quinidine sulfate in three to five grain doses at three hour intervals may prevent the occurrence of disastrous arrhythmias (auricular fibrillation, flutter, or ventricular fibrillation).

Coramine, by hypodermic, should be cautiously used. Although it has been shown to produce an increased coronary blood flow, the elevation of blood pressure associated with its hypodermic use is not desirable in the acute phase of a coronary thrombosis.

Atropine sulfate is of questionable value. Some workers have claimed an increased coronary flow due to the increased heart rate caused by vagal release.

Digitalis is definitely contraindicated in acute coronary thrombosis unless the patient has developed congestive heart failure or auricular fibrillation with a rapid ventricular rate. With either of these complications it should be cautiously used.

Other circulatory stimulants such as adrenalin, caffeine, and strophanthin should be avoided entirely unless the degree of circulatory shock demands their use. Even then, small doses cautiously used may be enough to overstimulate the ventricle and produce a fatal complication. Glycocol has been used by some to relieve the extreme exhaustion that develops in severe attacks.

Summary

1. One hundred white patients with coronary occlusion are reported. This includes consecutive patients seen and followed in private practice since 1930.

2. There was an immediate mortality of 12 per cent and a total mortality of 34 per cent.

3. Twenty-five of these patients had subsequent second or third attacks of coronary thrombosis.

4. Occupations involving executive capacities or considerable individual initiative were most frequent.

5. Overworry, overwork, and overeating were the most commonly occurring habit excesses.

6. Obesity, chronic cholecystitis, and diabetes mellitus were the most commonly associated diseases.

7. Physical exertion, bed rest, large meals, and emotional upsets were the most frequent events associated with the immediate attack.

8. Circulatory collapse and embolic phenomena were the most common complications of the immediate attack.

9. Angina pectoris, before and after the attack of coronary occlusion, was more common than no angina before or after the attack.

10. Referred pain was most common in the upper extremities and epigastrium, but was found in all levels from the mastoids to the lumbar region. Abdominal distress occurred in 50 per cent.

11. Hypertension before the attack was found in 41 per cent, and it persisted after the attack in 20 per cent.

12. Cardiac hypertrophy either before or after the attack was found in 59 per cent. Forty-one per cent had a normal sized heart. Arteriosclerosis in varying degrees was present in 97 per cent.

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PNEUMOCOCCAL MENINGITIS *

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Introduction

In 1896 Jemma [1] reported one of the earliest if not the first case of cure of pneumococcal meningitis. In spite of frequent subsequent reports of cures in the literature, this disease for many years has been thought to be almost always fatal. Goldstein and Goldstein [2] made an exhaustive study of the literature in 1927 and reported that "there are on record in the literature about 150 cases of recovery from proved pneumococcal meningitis." The recent increase in the frequency of reports of cures seemed to justify a review of the literature and especially an evaluation of the various methods of therapy employed. These methods were carefully analyzed and evaluated in the hope of disclosing some common denominator which would give the clue to the successful treatment of this disease. This review and an analysis of the cases of pneumococcal meningitis seen at the Cincinnati General Hospital in the period from 1936 through 1941 form the basis of this report.

Experimental

Several investigators have succeeded in producing this disease in animals, and have thereby contributed considerably to our understanding of its human counterpart. Stewart,[3] after discarding cats and rabbits, found the dog to be a suitable experimental animal. He succeeded in reproducing the disease in this animal by the intracisternal inoculation of virulent pneumococci. With Type I infections the picture presented was that of a rapidly spreading, fibrino-purulent leptomeningitis which involved all regions of the meninges as early as 24 hours after infection. In some animals, superficial encephalitis with invasion of the choroid plexuses was present; in others, the cord dura was invaded, the spinal nerve roots were involved, and there was an inflammatory process in the epidural fat. Especially remarkable, and important from the standpoint of treatment, was the high incidence of central cord involvement or even of suppurative myelitis in a large series of dogs infected with Type I pneumococci. In several instances this worker was able to effect cures by cisterno-lumbar lavage and the intrathecal introduction of an optochin-serum mixture. He thought it extremely important to bring

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all parts of the meninges into frequent contact with the therapeutic agent; when such contact was not complete "reinfection" was almost inevitable.

Stewart's [3] efforts with Type II infections were equally successful in reproducing the disease. He found, however, that Type II pneumococcal meningitis in dogs was characterized by the early production of a heavy fibrinous exudate and a consequent tendency toward the development of subarachnoid "blocks." The exudate tended to involve the walls and perivascular sheaths of deeply penetrating vessels, with subsequent parenchymatous softening and brain or cord abscesses. The lateral ventricles appeared to be a point of election, and hydrocephalus occurred early. Central myelitis was common and also appeared early in the disease. Employing a technic similar to that used in Type I infections, he was unable to effect any cures in canine Type II pneumococcal meningitis.

Kolmer and his associates [4] produced meningitis experimentally in rabbits and treated the animals with intrathecal injections of ethylhydrocuprein alone, and in conjunction with the homologous serum. They were able to reduce the mortality only slightly even though treatment was begun a few hours after infection. They, too, discarded the rabbit and selected the dog as a more suitable animal for pneumococcal experimentation. Following their production of the disease in dogs, they employed various antiseptics and antibodies as therapeutic agents but found none to be of eminent value. They did feel, however, that the lavage of the ventricular system was effective and that this might be combined with intrathecal administration of specific antibody or ethylhydrocuprein. Later, they reported cures in animals following the intracarotid and intracisternal injection of a mixture of Huntoon's antibody and ethylhydrocuprein. More recently Kolmer [4a] showed that sulfanilamide administered to these artificially infected animals prolonged their lives.

Gross and his collaborators [5, 5a] have reported the production of pneumococcal meningitis in rats after the intracranial inoculation of broth cultures of pneumococci. The disease produced in these studies very closely resembled that produced in dogs. Encephalitis occurred in more than half of the untreated animals. Pus was found in the cerebral ventricles in two-thirds of the rats at necropsy. In these animals, too, pus in the central canal or frank myelitis was found very frequently, occurring in about 40 per cent of the untreated animals. These workers employed various forms of therapy including the sulfonamides as well as specific serum. They found both sulfanilamide and sulfapyridine to be effective in reducing the mortality in the experimental disease; in Type I infections a combination of sulfanilamide by mouth and serum intraperitoneally was the most effective treatment. Type III antipneumococcus serum was without effect in treating the homologous infection. Increasing the size of the infecting dose or delay in instituting treatment diminished the likelihood of recovery. It is interesting to note that the animals which recovered showed very little evidence of a previously existing meningitis.

Diagnosis

The clinical picture of pneumococcal meningitis is not characteristic. If signs of meningitis supervene during the acute stage of pneumococcal pneumonia, the etiology of the former may be presumed to be pneumococcal. But pneumococcal invasion of the meninges does not produce either signs or symptoms which are pathognomonic.

The diagnosis of the disease should depend on an examination of the spinal fluid. The fluid is usually under increased pressure; in the majority of instances it lacks the usual transparency of normal spinal fluid, varying from a ground glass to a frankly purulent appearance. Further examination may show a decrease in the sugar content and an increase in protein and cellular elements. Almost always the predominant cell is the polymorphonuclear leukocyte, but Malaguzzi-Valeri [6] reported a case of meningitis due to mouse-avirulent Type I pneumococci in which the cellular reaction of the cerebrospinal fluid was lymphocytic.

Rhoads et al.[7] have rightly pointed out the error of the old dictum that meningitis is due to the meningococcus until proved otherwise. As with other bacterial diseases, the diagnosis of pneumococcal meningitis should depend on the demonstration of the organism. In more than half of the cases this can be done by a microscopic examination of the spinal fluid with the aid of suitable typing sera. If this fails, culture of the fluid will usually yield sufficient growth within a few hours to permit of the rapid identification of the organism. Identification of the pneumococcus by tinctorial methods has undoubtedly confused the picture of pneumococcal disease as reported in the literature, and should be deprecated. The finding of gram-positive organisms in pairs is not sufficient evidence for the diagnosis of pneumococcal meningitis; if such organisms are bile-soluble, the diagnosis may then be made. The adaptability of the "quellung" phenomenon of Neufeld has largely eliminated the necessity for bile-solubility determinations, and permits of a rapid species as well as type identification.

Any type of pneumococcus may cause meningitis. The so-called "higher" types of pneumococci are less likely to cause meningitis, but there is no reason to believe that these "higher" types are any less virulent after they have invaded the meninges. Table 1 will show the distribution of types of pneumococci causing meningitis in three large metropolitan hospitals in the United States, as compared with a large series reported by Ordman [8] from South Africa. Close study of the table reveals that the type-distribution of pneumococci causing meningitis follows no pattern closely as it does in pneumonia. The one apparent exception is the high incidence of Type III pneumococci in the three American series; the high incidence of Type III pneumococcus in ear and sinus infections and the predisposing influence of such diseases probably explains this exception. Fuller and more accurate reporting of pneumococcal disease in the future may disclose incidences, the significance of which is not apparent from such small series. It may be

worth while to point out the disparity in per cent incidences of Type I pneumococcus between the United States and South Africa. In the latter country this organism occurred to about the same extent in pneumonia as it did in meningitis. In this country, Type I causes pneumonia in 20 to 30 per cent of many large series, whereas in the three listed series of meningitis it was the causative agent in no more than 6 per cent. The typical nature of Type I pneumococcal pneumonia and the early use of potent sera may be

TABLE I

This table contains the type variations in three large general hospitals in the United States as compared with the distribution as reported by Ordman in South Africa. The New York figures are taken from the Harlem Hospital, and were kindly furnished by Dr. J. G. M. Bullowa. The Boston figures were reported from the Boston City Hospital by Dr. Maxwell Finland.

Type	Cincinnati	New York	Boston	South Africa
I	3	4	6	113
II	12	2	10	28
III	10	14	18	30
IV	5	5	5	
V	8	2	6	25
VI	6	6	2	
VII	6	10	7	18
VIII	4	7	12	
IX	1	2	2	
X	1	3	5	4
XI	1	0	3	
XII	5	5	2	26
XIII	0	0	2	
XIV	3	8	4	9
XV	0	0	0	
XVI	0	0	0	
XVII	1	1	1	
XVIII	1	6	3	
XIX	2	1	2	
XX	1	3	3	
XXI	0	1	0	
XXII	2	1	1	
XXIII	1	7		
XXIV		0		
XXV		2	1	7
XXVII			1	
XXVIII	1		1	
Above XXXII	2	2	2	
Untyped			1	Others 433
	76	92	100	697

responsible for the low incidence of this type of meningitis. The predominance of Type II and Type V pneumococci in the Cincinnati series is accounted for by the high incidence of endocarditis complicating pneumococcal pneumonia at the Cincinnati General Hospital; the frequency with which meningitis occurs as a terminal event in pneumococcal endocarditis has been reported previously.[9]

The infrequency with which more than one organism attacks any given part of the body at the same time is well exemplified in meningitis. This phenomenon is especially difficult to explain in meningitis which follows

head injuries and skull fractures. During the years 1936 to 1941 at the Cincinnati General Hospital, more than one kind of organism was never found in an infected spinal fluid. A rare instance of multiple infection is recorded in the literature. Some confusion may be caused by cross-reactions of typing sera of the higher types; one of our recently recovered patients had a pneumococcus in his cerebrospinal fluid which showed the "quellung" reaction with both Type XI and Type XVI sera; it was later identified * as a pneumococcus beyond Type XXXIII. Another patient had pneumococci in the spinal fluid which reacted with both Type VII and Type XXIV diagnostic sera, a characteristic of the so-called Type VII C pneumococcus. Reveno and McLaughlin [10] report one instance of bile-soluble encapsulated gram-positive diplococci which were agglutinated by both Type I and Type II sera; in all probability this phenomenon may have been accounted for by bivalent agglutinating sera. Recently, Erikkson and Sjöberg [11] have recorded a case of meningitis secondary to a head injury which was caused by Type II and Type XX pneumococci; the genuineness of the multiple infection is substantiated by the fact that the patient improved after Type II serotherapy and the homologous organisms disappeared from the cerebrospinal fluid whereas the Type XX organisms remained, and cure was not effected until Type XX antiserum was employed. Gaffney [14] reported a case of meningitis in an infant in which *H. influenzae*, Type VIII pneumococcus or both were grown from the cerebrospinal fluid on all occasions; unfortunately, cultures were not obtained at necropsy when the exudate showed only gram negative bacilli. Pray [33] has reported a case of osteomyelitis complicated by meningitis in which both a Type V pneumococcus and *Staphylococcus aureus* were isolated from both the blood and the spinal fluid.

The association of pneumococcus with the tubercle bacillus in the cerebrospinal fluid was recorded by Achard and Horowitz [15]; biological identification was not recorded. Two reports in the French literature [12, 13] attempted to show the association of meningococcus with pneumococcus in the causation of meningitis. Identification of the organisms in both reports was made on the basis of tinctorial and morphological characters alone.

Predisposing Factors

Pneumococcal meningitis may attack at any age (table 2). It has been reported in the newborn.[16, 17] The other extreme was exemplified by a patient, in our own series, who was more than 90 years of age. In our own experience the age incidence curve has resembled somewhat that seen in pneumococcal pneumonia in this community with a peak in the first decade and another in the fifth decade. A composite age incidence graph embracing all of the reported cases in the past 15 years shows more than half of the cases to occur before the age of 21; another peak does, however, occur in the fifth and sixth decades.

* Through the courtesy of Miss Frances Clapp of the Lederle Laboratories, Pearl River, New York.

The influence of sex on the incidence of bacterial diseases in general is not well understood. In our own series, the male: female ratio of 2: 1 prevails in pneumococcal infections of the meninges as well as of the lungs. A similar predominance of the infection among males is apparent in the reported cases.

There are recorded instances of pneumococcal meningitis among human beings of all colors and races, and there is very little evidence to show that any race shows any particular immunity or susceptibility. However, Ragiot,

TABLE II

	Died			Lived			Grand Total
	1927–36	1937–41	Total	1927–36	1937–41	Total	
Under 1 yr.	21	33	54	7	12	16	73
1–10	12	58	70	20	65	85	155
11–20	9	29	38	10	60	63	108
21–30	11	26	35	12	25	36	74
31–40	9	29	38	4	28	30	70
41–50	10	39	48	2	26	28	77
51–60	7	27	34	2	7	9	43
61–70	4	16	19	0	2	1	22
71–80	1	4	5	0	1	1	6
81–90	1	0	1	0	0	0	1
Male	54	154	204	32	135	161	375
Female	25	86	111	26	81	99	218
White	62	115	176	48	158	200	383
Colored	9	17	25	4	22	26	52
January	9	15	24	8	15	23	47
February	7	12	19	5	24	27	48
March	8	16	24	7	17	20	48
April	1	14	15	5	18	23	38
May	5	5	9	2	24	25	36
June	3	7	10	5	10	13	25
July	2	4	6	1	7	7	14
August	3	2	5	4	14	15	23
September	2	2	4	0	7	7	11
October	6	10	16	3	11	14	30
November	4	4	8	3	10	12	21
December	3	10	13	2	11	13	26

Delbove and Nguyen-van-Huong [18] do express the belief that the Annamites of Cochin-China are particularly good subjects for pneumococcal meningitis. The series at the Cincinnati General Hospital shows about the same ratio between white and negro patients as is seen in pneumococcal pneumonia.

The monthly incidence of the disease is shown in table 2. In a disease so closely related to diseases of the respiratory tract, such a distribution is not remarkable. The even distribution over the warmer months shows the effect of other factors than pneumococcal pneumonia in this disease.

The contagiousness of pneumococcal meningitis depends on the conditions favoring the dissemination of pneumococci. The disease occurred simultaneously in a man and his wife in the series at the Cincinnati General Hospital, but both patients had lobar pneumonia, in addition. Boyd, Baron.

and Schlachman [19] report the occurrences of primary Type II pneumococcus meningitis in a woman and her son, occurring one week apart.

Pneumococcal meningitis is frequently classified as either primary or secondary. Since the cranial contents are normally not exposed to a pneumococcus-containing environment, the concept of primary meningitis is difficult to sustain. Surprisingly small collections of pneumococcal infectious processes are capable of invading the meninges either by direct extension or by metastasis. It is not unlikely that "cryptogenic" describes the evolution of the process more accurately. In our own experience we have not seen a case of pneumococcal meningitis which came to necropsy which did not show at least one focus containing the homologous type of pneumococcus elsewhere in the body. In the series of collected cases comprising this report less than 25 per cent were reported as being primary in origin. In-

TABLE III

	Died			Lived			Grand Total
	1927–36	1937–41	Total	1927–36	1937–41	Total	
Blood culture							
Positive	20	58	74	1	31	31	110
Negative	6	27	33	5	60	57	98
Focus							
Head injury	4	1	5	3	8	11	16
Skull fracture	7	15	22	2	14	16	38
Otitis media	19	83	102	18	82	96	202
Pneumonia	10	26	36	7	8	14	51
Sinuses	2	12	14	1	14	15	29
Upper respiratory infection	0	10	10	2	17	19	29
Endocarditis	8	15	19	0	0	0	23
Eye	2	1	3	0	1	1	4
Primary	20	31	51	18	47	59	116

fections within, or injuries to, the head were responsible for more than half of this series of meningitis. Frequently trivial trauma to the skull may be the only possible explanation for the onset of the meningitis.[20, 21] Similarly, a long period may elapse between skull fracture and the onset of meningitis [22, 23, 24]; and not infrequently, skull fracture may not be apparent even when suspected.[25]

Otitis media and mastoiditis are listed as the cause of 202 out of 508 cases (table 3). Paranasal sinus disease, head injury and skull fracture accounted for 83 additional cases. Pneumonia accounted for 46 of our own cases, whereas it was recorded as the primary focus in only 51 of the collected cases. Pneumococcal endocarditis, rarely a primary disease, frequently terminates in meningitis.[9] The disease followed influenza and upper respiratory infections in only 5 per cent of the collected cases. Injuries to, or operations upon the eye very infrequently are followed by pneumococcal meningitis.[26, 27] Unusual cases following cellulitis of the ear,

pituitary tumor, lung abscess and pneumococcal peritonitis have been reported.[28, 7, 29, 30] Interestingly enough, lumbar puncture either as a diagnostic or a therapeutic measure was incriminated only twice as the predisposing cause of the meningitis.[31, 32] This confirms Pray's opinion that lumbar puncture was not a factor in causing the disease.[33]

The influence of previous infection or disease of the meninges is difficult to determine. Recurrent infections are not uncommon. Clark[34] reports a case in which the patient, an adult, recovered from an attack of pneumococcal meningitis but died two years later during a recurrence; the pneumococcus was not typed during the first attack, whereas a Type IV pneumococcus was responsible for the patient's death. One of our patients recovered from three attacks of pneumococcal meningitis within nine months. The organisms were of a different type in each instance being Types XVII, beyond XXXIII, and XXV respectively. Recently Craddock and Bowers[35] reported a patient who had four attacks of meningitis within a year, with recovery in each instance. Type XVII and Type XXVIII pneumococci were isolated during the first and third attacks respectively, whereas the spinal fluid cultures were sterile during the second and fourth. Three instances[36, 37, 38] of pneumococcal meningitis at varying intervals after recovery from hemolytic streptococcal meningitis appear in the literature; all recovered. And the French literature[39] records a case in which an adult recovered from two attacks of meningococcal meningitis, as well as from a pneumococcal infection of the meninges.

Treatment

The diversity of methods of therapy of pneumococcal meningitis, at least prior to 1937, is an indication of their inadequacy. Continuous subarachnoid drainage with intravenous hypotonic saline, cisterno-lumbar lavage, optochin and its derivatives, intravenous iodine and charcoal and specific serotherapy have all had their advocates, but no worker employing any single method has been able to report an impressive series of cures.

Table 4 represents a tabulation of the reported cases of pneumococcal meningitis in the available medical literature since 1926, exclusive of the cases listed in table 1. It is readily apparent that since 1936 there has been an increased interest in this disease, and many more cures are being effected. There is no evidence that the incidence of the disease is increasing; on the contrary, many epidemiological reports of pneumonia and otitis media claim a decreased incidence of complications since the advent of chemotherapy for these diseases. Both the augmented interest and the improved methods of treatment have undoubtedly been occasioned by the introduction of sulfanilamide and its derivatives. In table 5 are tabulated by types the reported recoveries since 1926, to which have been added five recoveries not previously reported from the Cincinnati General Hospital. Patients recovering from meningitis but dying shortly thereafter of other diseases

are not included. Scott[40] and Toomey and Roach[41] have reported recoveries from meningitis followed within a few weeks by death from pneumococcal endocarditis due to the homologous organism; one patient in our own series recovered from Type XIV pneumococcal meningitis, but died three weeks later of pneumococcal endocarditis.

TABLE IV

Type	Died		Lived		Grand Total
	1927–36	1937–41	1927–36	1937–41	
I	5	25	4	21	55
II	6	2	2	6	16
III	18	53	8	42	121
IV	2	12		10	24
V		4		10	14
VI		11		8	19
VII		8		7	15
VIII		5		4	9
IX		2		1	3
X		6		3	9
XI		1		1	2
XII	2	1		1	4
XIII		1		6	7
XIV		7		3	10
XV		0		2	2
XVI		1		0	1
XVII		0		2	2
XVIII		12		10	22
XIX		4		7	11
XX		0		4	4
XXI		2		1	3
XXII	1	2		0	3
XXIII		3		4	7
XXIV		1		0	1
XXV		1		3	4
XXVII		1		1	2
XXVIII		1		4	5
XXIX		2		3	5
XXXI		2		3	5
XXXII				1	1
Above Group XXXII		5		2	7
IV	13	6	4	6	29
Untyped	39	74	44	58	215
Total	86	255	62	234	637

A review of this table shows that a sulfonamide was used alone in 102 of the cases, whereas a sulfonamide and some other drug, or operation were employed in 25 additional cases. Serum was the only therapeutic agent of import in 24 cases, and serum and sulfonamide therapy were combined in 70 cases. In five cases serum, sulfonamide and some other drug were administered. Thus, in more than 85 per cent of the recovered cases one of the sulfonamides or serum or both were employed as the significant therapeutic agents. Twelve of the patients recovered without any therapy which might conceivably be called specific, and five others recovered after surgical drainage of the primary focus.

TABLE V

Reference No.	Blood Culture	Age	Focus	Treatment
			Type I	
10	—	20	Head injury	Bivalent serum
71	—	28	Skull fracture	Serum
72	—	1	Upper respiratory infection	Daily lumbar puncture
73	Neg.	57	Otitis media	Serum
74	—	16	Primary	Prontosil
75	—	26	Primary	Prontosil
36	—	17	Otitis media	Sulfapyridine
76	—	7	Primary	Sulfapyridine
77	—	11	Primary	Sulfanilamide
49	Pos.	8	Otitis media	Sulfanilamide, sulfapyridine and serum
51	Neg.	7	Otitis media	Sulfapyridine
7	Pos.	15	Primary	Sulfanilamide and serum
43	Neg.	44	Otitis media	Sulfapyridine, serum and mastoidectomy
65	—	<1	Pneumonia	Sulfapyridine and serum
78	—	47	? Sinus	Sulfanilamide and sulfapyridine
79	—	—	Primary	Sulfanilamide, sulfapyridine and serum
80	—	24	Otitis media	Prontosil album and soluseptazine
6	—	<1	Primary	None
61	—	23	Otitis media	Sulfanilamide and mastoidectomy
81	—	12	Otitis media	Serum and mastoidectomy
229	Pos.	46	Otitis media	Sulfapyridine and serum
239	Neg.	13	Otitis media	Sulfapyridine and serum
240	—	14	Otitis media	Sulfapyridine and serum
241	Neg.	35	Primary	Sulfapyridine
241	Neg.	25	Primary	Sulfapyridine
			Type II	
82	—	31	Primary	Convalescent serum
83	—	<1	Pneumonia	Serum
19	—	43	Primary	Serum
19	—	14	Primary	Serum, Prontosil, and hydroxyethylapocupreine
84	Neg.	5	Otitis media	Mastoidectomy and hyperthermia
11	—	24	Head injury	Sulfapyridine and specific sera (II and XX)
230	—	1	Upper respiratory infection	Sulfathiazole
241	Neg.	19	Primary	Sulfapyridine
			Type III	
85	Neg.	7	Otitis media	Antimeningococcus serum
86	—	16	Otitis media	Serum and radical mastoidectomy
87	—	10	Otitis media	Mastoidectomy
88	—	30	Primary	$KMnO_4$ enemata
89	—	35	Otitis media	Forced drainage and radical mastoidectomy
90	Neg.	50	Eye	Sulfathiazole and serum
31	—	32	? Spinal anesthesia	Antimeningococcus serum
91	—	35	Otitis media	Sulfapyridine, serum and mastoidectomy
92	—	40	Otitis media	Sulfapyridine, and petromastoidectomy
93	—	32	Otitis media	Labyrinthectomy
94	Neg.	15	Otitis media	Mastoidectomy
64	—	5		Sulfanilamide and mastoidectomy
95	Neg.	<1	Otitis media	Sulfapyridine
96	—	11	Otitis media	Sulfapyridine and serum

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Type III (*Continued*)	
49	—	39	Otitis media	Sulfapyridine, serum and mastoidectomy
50	—	36	Otitis media	Sulfapyridine
97	Neg.	11	Otitis media	Sulfanilamide, mastoidectomy and hydroxyethylapocupreine
97	Neg.	8	Otitis media	Sulfanilamide, mastoidectomy and hydroxyethylapocupreine
51	Neg.	45	Otitis media	Sulfapyridine
51	Pos.	11	Otitis media	Sulfapyridine
37	Pos.	6	Otitis media	Sulfathiazole and serum
43	Neg.	48	Otitis media	Sulfapyridine, serum and petrosectomy
98	—	39	Otitis media	Prontosil, serum and radical mastoidectomy
52	—	9	Otitis media	Sulfanilamide
99	—	48	Otitis media	Sulfapyridine
100	—	30	Primary	Sulfapyridine
54	—	15	Otitis media	Sulfapyridine, serum and apicectomy
101	—	18	Otitis media	Sulfapyridine
42	Neg.	10	Otitis media	Sulfanilamide and mastoidectomy
102	Neg.	25	Upper respiratory infection	Sulfapyridine
103	—	42	Sinus	Prontosil and operation
104	—	17	Otitis media	Sulfanilamide and mastoidectomy
105	—	54	Otitis media	Sulfanilamide
106	—	60	Otitis media	Sulfanilamide
107	—	40	Otitis media	Sulfanilamide
108		3	Sinus	Sulfanilamide and drainage of sinuses
109	—	17	Mastoid	Serum and mastoidectomy
110	—	35	Mastoid	Sulfapyridine, serum and mastoidectomy
44	Pos.	46	Conjunctivitis	Sulfapyridine, serum and sulfadiazine
111	—	6	Otitis media	Sulfapyridine
111	—	7	Otitis media	Sulfapyridine
111	—	6	Otitis media	Sulfapyridine
112	Pos.	22	Otitis media	Sulfapyridine and serum
112	Neg.	12	Otitis media	Sulfapyridine and serum
113	Neg.	46	Mastoid	Sulfathiazole and sulfamethylthiazole
231	Neg.	7		Sulfathiazole
241	Neg.	18	Primary	Sulfapyridine
			Type IV	
114	—	7	Upper respiratory infection	Sulfapyridine
43	Pos.	1	Otitis media	Sulfapyridine, serum and drainage of brain abscesses
43	—	8	Primary	Sulfapyridine and serum
115	Pos.	—	Nose fracture	Continuous subarachnoid drainage
116	—	9	Sinus	Sulfapyridine, and radical frontal operation
32	Neg.	5	Otitis media	Sulfanilamide and serum
117	Neg.	40	Primary	Daily lumbar punctures
118	Neg.	19	Primary	Sulfanilamide and serum
108	Pos.	1	Primary	Sulfapyridine and serum
119	Pos.	6	Otitis media	Sulfapyridine and serum
231	Neg.	5		Sodium sulfapyridine and serum
239	Neg.	62	Otitis media	Sulfanilamide and serum
			Type V	
97	Neg.	9	Otitis media	Sulfanilamide, mastoidectomy, and hydroxyethylapocupreine

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Type V (*Continued*)	
51	Neg.	11	Otitis media	Sulfapyridine and mastoidectomy
43	Pos.	13	Upper respiratory infection	Sulfapyridine, serum and mastoidectomy
120	Neg.	9	Otitis media	Prontosil and mastoidectomy
121	—	10	Otitis media	Sulfapyridine and serum
41	Neg.	12	Otitis media	Sulfapyridine and serum
41	Neg.	15	Upper respiratory infection	Sulfanilamide and sulfapyridine
41	Neg.	29	Otitis media	Sulfanilamide and sulfapyridine
122	Neg.	6	Otitis media	Sulfapyridine, serum and operation
			Type VI	
123	Neg.	2	Otitis media	Sulfanilamide and serum
25		6	Nose fracture	Sulfapyridine and serum
7	Pos.	8	Pneumonia	Sulfanilamide and serum
32	Neg.	16	Sinus	Sulfanilamide and serum
124	Pos.	<1	Primary	Sulfapyridine and serum
232	Pos.	54	Nasal polyp	Sulfapyridine and serum
233	—	42	Skull fracture	Sulfathiazole and sulfapyridine
234	Pos.	5	Skull fracture	Sulfapyridine
			Type VII	
125	—	20	Sinus	Sulfanilamide, serum and radical frontal operation
59	Pos.	33	Pneumonia	Sulfanilamide and serum
42	Neg.	8	Skull fracture	Sulfanilamide and serum
61	—	48	Pneumonia	Sulfanilamide, serum and continuous drainage
126	—	19	Otitis media	Sulfapyridine, rubiazol, soluseptazine, and mastoidectomy
241	Neg.	17	Primary	Sulfapyridine
231	Neg.	12		Sodium sulfapyridine
			Type VIII	
119	Pos.	<1	Primary	Sulfapyridine and serum
112	—	13	Primary	Sulfanilamide and sulfapyridine
234	Pos.	—		Sulfadiazine and serum
243	Neg.	36	Pneumonia	Sulfadiazine
			Type IX	
51	Neg.	32	Upper respiratory infection	Sulfapyridine
			Type X	
7	Pos.	42	Primary	Sulfapyridine and serum
127	—	7	Primary	Sulfapyridine
229	—	19	Otitis media	Sulfapyridine
			Type XI	
128	—	5	Upper respiratory infection	Sulfanilamide, sulfapyridine and serum

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Type XII	
51	Pos.	35	Primary	Sulfapyridine
			Type XIII	
21	—	27	Mastoid	Sulfanilamide, serum and soluseptazine
32	Neg.	15	Otitis media	Sulfanilamide and serum
41	Pos.	31	Pneumonia	Sulfapyridine and serum
129	Neg.	35	Mastoid	Sulfanilamide, azosulfamide and radical mastoid
231	Neg.	6		Sodium sulfapyridine
235	—	40	Head injury	Sulfapyridine (1 relapse)
			Type XIV	
130	Neg.	16	Skull fracture	Sulfanilamide
131	—	1	Primary	Sulfanilamide, sulfapyridine and serum
132	—	10	Upper respiratory infection	Sulfapyridine and serum
			Type XV	
133	Neg.	22	Sinus	Sulfanilamide and daily lumbar punctures
43	—	14	Skull fracture	Sulfapyridine
			Type XVII	
7	Pos.	15	Otitis media	Sulfanilamide and serum
119	Neg.	10	Otitis media	Sulfapyridine and serum
35	—	32	Primary	Sulfapyridine
			Type XVIII	
35	Pos.	14	Primary	Sulfapyridine and serum
43	Neg.	8	Otitis media	Sulfanilamide, sulfapyridine, azosulfamide, and mastoidectomy
38	—	19	Otitis media	Sulfapyridine and serum
134	Neg.	5	Primary	Sulfapyridine and serum
79	—	30	Primary	Sulfanilamide and sulfapyridine
42	Neg.	19	Brain tumor	Sulfanilamide
108	—	—	Sinus	Sulfapyridine and serum
33	Pos.	6	Otitis media	Sulfanilamide and serum
231	Neg.	11		Sodium sulfapyridine and serum
231	Neg.	3		Sodium sulfapyridine and serum
			Type XIX	
63	—	7	Primary	Sulfanilamide, sulfapyridine and serum
137	Neg.	23	Primary	Sulfapyridine
43	Pos.	45	Otitis media	Sulfapyridine and serum
42	Neg.	7	Skull fracture	Sulfanilamide and serum
135	Pos.	11	Otitis media	Sulfapyridine, serum and mastoidectomy
136	—	2	Otitis media	Sulfapyridine and mastoidectomy
137	—	60	Otitis media	Sulfapyridine and serum

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Type XX	
138	Neg.	18	Sinus	Radical frontal operation
139	Neg.	14	Primary	Sulfapyridine and serum
55	—	41	Upper respiratory infection	Sulfapyridine
140	—	42	Otitis media	Sulfapyridine, serum and sulfanilamide
			Type XXI	
141	Pos.	9	Primary	Sulfapyridine and serum
			Type XXIII	
49	Pos.	53	Skull fracture	Sulfapyridine and serum
40	Neg.	14	Primary	Sulfapyridine
51	Pos.	49	Primary	Sulfapyridine
7	Neg.	12	Skull fracture	Sulfapyridine and serum
			Type XXV	
142	Pos.	49	Upper respiratory infection	Sulfapyridine
51	Pos.	34	Pneumonia	Sulfanilamide and sulfapyridine
119	Neg.	11	Primary	Sulfathiazole
			Type XXVII	
143	—	11	Primary	Sulfanilamide
			Type XXVIII	
42	Neg.	17	Head injury	Sulfanilamide
42	Neg.	13	Primary	Sulfanilamide and serum
35	—	32	Primary	Sulfapyridine
144	Pos.	49	Sinus	Sulfapyridine and serum
			Type XXIX	
130	Neg.	42	Brain operation	Sulfanilamide and dural repair
32	Neg.	22	Nose operation	Sulfanilamide and serum
145	—	25	Pneumonia	Sulfapyridine and serum
			Type XXXI	
7	Neg.	76	Primary	Sulfanilamide and serum
32	Neg.	50	Sinus	Sulfanilamide, serum and operation
232	—	—		Sulfonamide
			Type XXXII	
112	Neg.	12		Sulfapyridine and serum

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Types Above XXXII	
43	Neg.	46	Primary	Sulfapyridine
119	Neg.	10	Otitis media	Sulfathiazole and serum
236	—	10	Sinus	Sulfapyridine
			Group IV	
146	Neg.	11	Otitis media	Serum and Pregl's iodine
147	—	15	Otitis media	Vaccine and daily lumbar puncture
148	Neg.	42	Sinus	Continuous drainage
149	—	5	Pneumonia	Serum
93	—	50	Dural repair	—
150	Neg.	13	Otitis media	Sulfanilamide and mastoidectomy
151	—	38	Primary	Sulfapyridine
100	—	28	Upper respiratory infection	Sulfapyridine
152	Pos.	6	Otitis media	Sulfapyridine
237	Neg.	41	Osteoma of skull	Sulfapyridine
			Untyped	
153	—	—	Mastoid	Mastoidectomy and urotropin
154	—	13	Primary	2% optochin
155	—	6	Primary	Serum
156	—	1	Otitis media	Serum and urotropin
157	—	1	Primary	None
158	—	8	Primary	Serum
159	—	5	Otitis media	5% mercurochrome
160	—	27	Primary	Bivalent serum
161	—	1	Pneumonia	Polyvalent serum, vaccine and "fixation" abscess
162	—	21	Otitis media	Serum, "fixation" abscess and mastoidectomy
163	—	1	—	Serum
164	—	25	Primary	Serum and optochin
165	—	5	Primary	Multiple punctures and antimeningococcus serum
166	—	43	Primary	Bivalent serum
167	—	—	Otitis media	Pn. I serum, and daily lumbar punctures
168	Pos.	36	—	Polyvalent serum and daily lumbar punctures
169	—	22	Otitis media	Urotropin and radical mastoidectomy
170	Neg.	18	Primary	Serum and daily lumbar punctures
171	—	26	Primary	Mixed serum
172	—	5	Primary	Serum
34	—	29	Head injury	Daily lumbar punctures
173	—	25	Primary	Serum and mercurochrome
174	—	59	Primary	None
175	—	21	Skull fracture	Huntoon's antibody
176	—	3	Pneumonia	Daily drainage of subarachnoid fluid
177	—	16	Pneumonia	Felton's serum
178	—	1	—	None
179	—	13	Otitis media	Daily lumbar punctures
180	—	1	Primary	Serum
181	—	9	Otitis media	Serum
182	—	5	Primary	Serum
183	—	21	Pneumonia	Serum
183	—	10	Pneumonia	Serum
184	—	5	—	Optochin
185	—	—	Otitis media	Mastoidectomy
186	—	2	Head injury	None

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Untyped (*Continued*)	
187	—	6	Primary	Serum
188	—	14	Primary	Haptinogen
188	—	28	Primary	Haptinogen
188	—	19	Upper respiratory infection	Haptinogen
189	—	1	Primary	None
190	—	—	Primary	Hydroxyethylapocupreine
191	—	8	Otitis media	Mastoidectomy
192	—	9	Otitis media	Daily lumbar punctures
193	—	5	—	Sulfanilamide and serum
193	—	9	—	Sulfanilamide and serum
193	—	6	—	Sulfanilamide
194	—	4	Otitis media	Rubiazol, neococcyl, soluseptazine and serum
24	—	8	Skull fracture	Sulfapyridine, septoplix and dural repair
195	—	8	Otitis media	Sulfapyridine
196	—	1	Upper respiratory infection	Soluseptazine, sulfapyridine, and daily lumbar punctures
196	—	6	Otitis media	Sulfapyridine and soluseptazine
197	—	3	Otitis media	Sulfapyridine
198	—	3	Upper respiratory infection	Sulfapyridine
199	—	2	Otitis media	Serum and optochin
200	—	5	Primary	Polyvalent serum
47	—	5	Otitis media	Sulfanilamide and antimeningococcus serum
201	Neg.	15	Otitis media	Benzyl sulfanilamide and mastoidectomy
76	—	42	Sinus	Sulfapyridine
202	—	4	Primary	Sulfapyridine and serum
203	—	53	Primary	Sulfapyridine and "1162F"
204	—	37	Primary	Sulfapyridine
39	—	26	Primary	Sulfapyridine
205	—	35	Sinus	Operation and intravenous charcoal
49	—	52	Skull fracture	Sulfapyridine
206	—	15	Otitis media	Sulfapyridine, soluseptazine and streptalbumin
207	—	17	Otitis media	Sulfapyridine and radical mastoidectomy
208	—	39	Primary	Sulfanilamide and electrargol
209	—	8	Primary	Prontosil
210	—	7	Upper respiratory infection	Sulfapyridine
211	—	14	Primary	Sulfapyridine, soluseptazine and bivalent serum
212	—	24	Upper respiratory infection	Sulfapyridine
53	—	34	Primary	Sulfapyridine
213	—	18	Influenza	Sulfapyridine
213	—	27	Primary	Sulfapyridine
214	—	39	Otitis media	Sulfapyridine, soluseptazine and mastoidectomy
215	—	6	—	Sulfapyridine
215	—	13	—	Sulfapyridine
216	—	1	Primary	Sulfanilamide and serum
217	Neg.	19	Primary	Prontosil, and frequent lumbar punctures
218	—	11	—	Sulfapyridine and forced drainage
218	—	7	—	Sulfapyridine and forced drainage
219	—	27	Otitis media	Human serum
220	—	1	—	None
221	—	24	Primary	Sulfapyridine
222	—	30	Nose fracture	Soluseptazine
223	—	1	Otitis media	Septoplix
224	—	20	—	Serum and vaccine
62	—	24	Skull fracture	Elevation of bone, numerous lumbar punctures

TABLE V (*Continued*)

Reference No.	Blood Culture	Age	Focus	Treatment
			Untyped (*Continued*)	
225	—	2	Upper respiratory infection	Sulfanilamide
226	—	64	Pneumonia	Sulfapyridine and "1162F"
226	—	48	Primary	Sulfapyridine and "1162F"
227	—	39	Otitis media	Sulfapyridine
228	Neg.	27	—	Sulfapyridine
126	—	32	Otitis media	Sulfapyridine and mastoidectomy
231	Neg.	20		Sodium sulfapyridine
238	—	22	None	Sulfapyridine
242	Pos.	19	Primary	Sulfapyridine
244	—	15	Otitis media	Sulfapyridine
245	—	<1	—	Sulfapyridine
245	—	<1	—	Sulfapyridine
245	—	<1	—	Sulfapyridine

The hope of discovery of some common denominator of these recoveries occasioned this review, yet the key to the cure of pneumococcal meningitis is not so apparent. It is certain that the sulfonamides either alone or in combination with specific serum seem to be curative in certain cases of pneumococcal meningitis. Finland, Brown, and Rauh,[42] in 1938, were the first to advocate a combined régime of serum and sulfonamide therapy in this disease, and reported six consecutive cures employing this method of treatment. Similarly, Neal and her associates [43] and Rhoads et al.,[7] who reported 10 and seven recoveries respectively, felt that combined therapy offered the greatest hope of success. The six patients who recovered at the Cincinnati General Hospital received serum as well as one of the sulfonamides. The choice of sulfonamide does not appear to be especially important; sulfapyridine has been employed most frequently because of its bacteriostatic superiority over sulfanilamide, and because its diffusion into the cerebrospinal fluid is greater than that of sulfathiazole. Recently sulfadiazine has been employed in curing several patients with pneumococcal meningitis.[44, 234, 243] However, the poorer diffusibility of sulfathiazole is not a necessary contraindication to its use, for it has been shown to be a very effective agent in the treatment of meningococcal meningitis [45] as well as staphylococcal meningitis.[46] In our own experience, three of the patients recovered after receiving the latter drug and the lower blood and cerebrospinal fluid concentration did not seem to be disadvantageous. Dosage should be determined by the conditions surrounding the individual case. The early administration of the chemical by the intravenous route, usually in the form of the sodium salt, is accepted and recommended by most workers because the lag due to absorption is thereby obviated; of course, in comatose patients this method is almost compulsory. Further time may be gained by an initial intrathecal injection of a solution of the drug; Neal and her as-

sociates [43] found a 2 per cent solution of sodium sulfapyridine feasible for this purpose and without untoward reaction. After attaining a desired level, further therapy can be continued by the intravenous or oral route. In general, therapy should not be discontinued for several days after the cerebrospinal fluid has been sterilized. Recrudescences in pneumococcal meningitis are notorious [43, 47, 48, 49, 50, 51, 52, 53, 54, 55]; most frequently, inadequate treatment is the cause, but the possibility of undrained or unresolved purulent foci should always be kept in mind.

In a few well-authenticated cases, the organisms have apparently become resistant or "fast" during the course of treatment.[29, 56, 57, 58] Further chemotherapy is usually useless then, and serum treatment should be employed without further delay.

Theoretically, a combination of serum therapy and chemotherapy is not unsound. There are still too few cases on record to determine whether such a combination of therapy is more effective than chemotherapy alone. Several workers have reported improvement of their patients under chemotherapy but without cure until serotherapy had been employed. At the present time, it seems the wiser plan to give the patient the benefit of both types of treatment.

The amount of serum cannot be stated dogmatically. Probably 100,000 units will suffice for most cases. If tests for serum adequacy are available and reliable, they could well be employed. Otherwise, the total amount of serum should depend on many factors, probably the most important being the age of the disease, the extent of pneumococcal disease elsewhere in the body, and the degree of bacteremia. Query [59] used 600,000 units in treating a case secondary to pneumonia and empyema, and Rhoads et al.[7] employed an equal amount in curing a patient with primary meningitis. Finland, Brown and Rauh [42] felt that the intrathecal injection of large amounts of concentrated serum might be harmful, but advised the subarachnoid administration of human serum containing specific antibody as well as complement. Neal et al.[43] also employed the subarachnoid route, as well as the intravenous, for serum administration. The importance of this factor is by no means clear. Our own recovered patients as well as many others reported in the literature did not receive serum by this route.

The elimination or drainage of accessible purulent foci in the treatment of pneumococcal infections is fundamental, and meningitis affords no exception. The literature abounds with cases exemplifying failure to heed this rule with the consequent reinfection and ultimate death of the patient. An undrained middle ear,[60] sinus or mastoid may frequently be asymptomatic, yet be the cause for the continuance of the infection. And in meningitis secondary to pneumonia, an empyema of the pleural cavity may be easily overlooked.

The frequency with which lumbar punctures should be performed has long been a moot point. At one time continuous drainage of the subarachnoid space was recommended in the treatment of pneumococcal as well as

other forms of bacterial meningitis. The cases collected in this report exemplify all variations in this respect. Slaughter and Sydenstricker[61] cured two patients with continuous drainage of the subarachnoid space; Toone and Higginbotham's[62] patient recovered after 92 subarachnoid taps in the course of 129 days, whereas Leichenger and Abelson[63] performed only one lumbar puncture. The trend seems definitely to be in the direction of fewer subarachnoid drainages. In our own experience lumbar punctures seem to be indicated for diagnosis and as guides to adequacy of treatment.

The effect of the sulfonamides as a prophylactic requires further observation. Theoretically, it seems to be sound and judicious to employ this drug locally after operations on the skull or following skull fractures. On the other hand, several workers report the onset of meningitis during the course of sulfonamide therapy for the primary infection.[25, 48, 64, 65, 66] Kolmer and Amano[67] suggested the specific prophylaxis of pneumococcal meningitis by means of vaccine. Goldman and Hirschberger[68] applied the principle clinically, and thought it to be of value in reducing the intracranial complications of mastoiditis; the series was not well controlled. In view of the uncertainty of development of active immunity against the pneumococcus by vaccines, prophylaxis by this method can scarcely be recommended very seriously.

Results of Treatment

There is very little doubt that pneumococcal meningitis formerly was a very fatal disease. There is no record of a recovery at the Cincinnati General Hospital prior to 1937. In most communities the death rate has been considered to be in excess of 95 per cent.

Undoubtedly, the case mortality rate of pneumococcal meningitis has been lowered. It is hazardous to be more specific in evaluating a series of collected cases, for the case reports of recoveries are much more likely to be published than are the failures of therapy.

It appears, however, that this saving of lives affects all age groups, and especially those between one and 20. The prognosis in infancy remains grave. The improved method of treatment has no predilection for a certain type of pneumococcus, and there is no evidence that any certain type is especially resistant to this therapy. As a matter of fact, the percentile increase of cures of Type III pneumococcal meningitis is striking in view of the mortality of Type III pneumococcal pneumonia. Meningitis secondary to infections within the head or injuries to the head has been more amenable than that secondary to pneumonia; this might be expected because the primary focus is more likely to yield to direct treatment and because bacteremia is less likely to become a factor.

Neal, Applebaum and Jackson,[43] in an analysis of their own 30 cases, concluded that bacteremia had no particular bearing on the outcome of the disease. An analysis of this series of 637 cases compels the opposite con-

clusion. Of the 296 recovered cases, only 31 had positive cultures, 57 had negative reports, and the remainder were either uncultured or not reported. Of the 341 patients who died, 74 had bacteremia, 33 had negative blood cultures, and the remainder were not cultured. Bacteremia is of paramount prognostic import in pneumococcal pneumonia,[69] and probably is a big factor in determining the outcome of pneumococcal disease of the meninges.

Stewart, as well as Kolmer and more recent investigators, predicted the difficulties of treatment of this disease in their work on animals. They noted the tendency of the pneumococcus to provoke the early outpouring of a massive fibrinous exudate. The discovery of highly diffusible bacteriostatic drugs undoubtedly adds to the humoral defense of the body in that respect. They also noted that recovery did not occur in experimentally-produced disease if there was more than a short interval between onset of the disease and institution of therapy. Similarly, in the human disease earlier diagnosis is necessary if best results are to be obtained.

Robertson[70] in England thinks that the case mortality rate of the disease might be 25 per cent or less at present, citing his recent experience as proof. Such optimism seems unjustified from this review; in this country there is no reason to believe that such results are approximated by even a wide margin.

Summary

A review of the available literature since 1926 concerning pneumococcal meningitis is presented.

It is essentially a disease of younger people but may occur at any age.

It usually follows disease of the ear, mastoid and sinuses, pneumonia, or injuries to the skull; frequently, the disease appears to be primary in origin.

Important factors in determining the prognosis are: age of patient, duration of disease before treatment, presence or absence of bacteremia, and the extent and distribution of primary foci.

Successful treatment depends, in the main, on prompt and vigorous sulfonamide therapy, intravenous injection of specific concentrated serum, and the drainage of accessible foci of pneumococcal pus.

The disease continues to have a serious prognosis, and demands early recognition if recovery is to occur.

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PRIMARY AMYLOIDOSIS; A REPORT OF THREE CASES *

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PRIMARY or idiopathic amyloidosis is a rare and poorly understood disease, although it was recognized as far back as 1856, when it was described by Wilks.[1] In the Guy's Hospital Report of that year, Wilks brought attention to this pathologic entity, which he named "lardaceous disease." Since his time, the number of reported autopsy-proved cases has been small. It is the purpose of this paper to add three cases to the literature and to make certain clinical observations concerning them.

Recently several American authors have published case reports of primary amyloidosis. In 1936 Kerwin [2] reported two cases, and in 1939 Koletsky and Stecher [3] reported one case and noted some 30 other cases in the literature. After that report, Binford [4] had one patient with proved primary amyloidosis, and more recently, Pearson, Rice, and Dickens [5] published two cases which they believed to be the first which had occurred in negroes. In 1930, however, Larsen [6] had noticed the occurrence of primary myocardial amyloidosis in a negro man 65 years of age.

In 120,785 admissions to the Medical and Surgical services of the Peter Bent Brigham Hospital during the period from April 12, 1913, to June 1, 1941, there were 35 cases diagnosed as amyloid disease. This diagnosis was proved in 23 out of 4,551 autopsies performed during this time. In 20 of these, amyloidosis was secondary to such chronic diseases as tuberculosis, syphilis, lung abscess, pyelonephritis, and various other forms of chronic suppuration. In only three cases was amyloidosis present without other major pathologic findings, and therefore, primary. The distinction between primary and secondary amyloidosis is well recognized and has been well defined by Reimann and others [7] and by Lubarsch.[8]

CASE REPORTS

Case 1. D. B., a 61-year-old Italian scissors-grinder, entered the hospital February 21, 1941, and was discharged March 2, 1941. His chief complaint was substernal pain and dyspnea of 6 months' duration. His family history was irrelevant. He had a past history of generalized rheumatism and fever of three days' duration at the age of 40, and a mild dry cough for years.

The present illness began six months before entry, with attacks of squeezing and gripping substernal pain with dyspnea. The pain radiated to the right upper quadrant and shoulder, and was definitely and exclusively related to exertion and relieved by rest. The attacks increased in frequency from two to four daily at the onset, to 12 to 14 on admission, and were severe enough to prevent his working during the two

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months prior to admission. He had progressively increasing edema of the lower extremities for one month before entering the hospital. Four months before admission, he awakened one morning to find both eyes black and blue, an egg-sized mass in the left axilla, and a purplish symptomless rash over the left arm and pectoral region. He had lost 20 pounds in six months. During the week before admission he had two spells of paroxysmal nocturnal dyspnea.

Physical Examination. The patient was a moderately obese Italian male in no apparent distress. The vital signs were normal, and his blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. There were large purpuric areas over the left upper arm, axilla, and left half of the thorax. His eyes, including the fundi, were normal. He had marked dental caries and pyorrhea. In the left axilla there was a firm, non-tender, partially fixed, lemon-sized mass with several neighboring, smaller, similar, discrete nodes. In the right axilla there were similar walnut-sized nodes. The inguinal nodes were only slightly enlarged. The heart seemed moderately enlarged to the left; the sounds were clear, regular, without murmurs. There were signs of fluid at the right lung base and many coarse râles at both bases. The abdomen was soft with no detectable ascites. A smooth, firm, tender liver edge was felt down a hand's breadth in the right upper quadrant, and a smooth, firm, non-tender spleen extended down a similar distance on the left. There was a 3+ soft edema of the sacrum, scrotum, and lower extremities. No venous distention was observed.

Laboratory Data. The blood Hinton and Wassermann reactions were negative. The urine on three examinations concentrated to 1.014. There was a small amount of protein once, and sediments were negative. Blood counts, smear, hemoglobin and hematocrit determinations were normal. The platelets numbered 136,000 per cubic millimeter. The clotting and bleeding times were normal, and the tourniquet test was within normal limits. Stools were negative for blood. The sputum was thick, green, and purulent; it was negative for tubercle bacilli. The serum non-protein nitrogen was 37 mg. per 100 c.c.; the icteric index was 5, and the total serum protein 6.1 grams per 100 c.c. The venous pressure was 110 mm. of water, the normal being 150 mm. Decholin circulation time was 33 seconds. An electrocardiogram showed mild left axis deviation, low electromotive force, and a P–R interval of 0.24 second with Lead IV normal. Roentgenologic examination showed the heart, especially the left ventricle, to be markedly enlarged, and the aorta tortuous. There was an irregular patch of consolidation at the right base and some fluid in the right costophrenic angle. A film of the abdomen was non-contributory.

Hospital Course. The vital signs remained normal throughout the patient's hospital course. Four days after admission biopsy of the left axillary mass was undertaken, and it was found to consist almost entirely of necrotic blood clot. One of the inguinal nodes was removed instead (figure 1). The next day there was considerable bleeding from the axillary wound, and the hemoglobin fell to 64 per cent (photoelectric method). Prothrombin time was found to be 37 seconds (normal control 23 seconds). The bleeding was controlled by pressure bandages, and 400 c.c. of whole blood were given cautiously. On the sixth day digitalis was begun, and by the ninth day he had received 1.3 grams orally. On the afternoon of the ninth day he complained of weakness and dyspnea, and his pulse became slow and irregular. The electrocardiogram now showed a slow, slightly irregular rhythm due to variation of the auricular pacemaker, but there were no other changes. That night he complained of severe, intermittent, epigastric pain. He vomited 200 c.c. of dark fluid material, which was guaiac positive. He became increasingly dyspneic and restless. His blood pressure fell to 70 mm. Hg systolic and 40 mm. diastolic, but the peripheral circulation remained good and the pulse did not rise over 72. He died in his sleep a few hours later.

Biopsy Diagnosis. Nodes from the axilla and groins showed a large amount of dense, homogenous material in walls of blood vessels and lymphatics and beneath the lining of the sinuses, consistent with amyloidosis of the lymph nodes (figure 1).

Clinical Diagnoses. Myocardial infarction due to arteriosclerotic coronary thrombosis, malignant lymphoma, possible Hodgkin's disease, possible gastrointestinal hemorrhage.

FIG. 1. *Case 1.* Biopsy of a lymph node (× 150). There is a large amount of dense homogenous material in the walls of the blood vessels and lymphatics and beneath the lining of the sinuses. This material is amyloid.

Postmortem Diagnoses. Generalized amyloidosis, cardiac hypertrophy and dilatation, purpura, chronic passive congestion of the viscera, focal hemorrhage and necrosis of the liver, dependent edema, hydropericardium, hydrothorax, pulmonary emphysema and atelectasis, pleural adhesions, diverticula of the colon, peritoneal adhesions, and left hydrocele.

The liver, spleen, kidneys, and blood vessels in every location except in the spinal cord showed deposition of amyloid material. The heart weighed 670 grams and was well dilated. The coronary arteries were tortuous and the lumina narrowed but otherwise showed no gross changes. Microscopic examination, however, showed that in the coronary vessels there were abundant subintimal deposits of hyaline material which had the characteristic staining properties of amyloid. This was also the case with material found within the epicardium, endocardium, and myocardium, as well as within the leaflet of the tricuspid valve (figure 2).

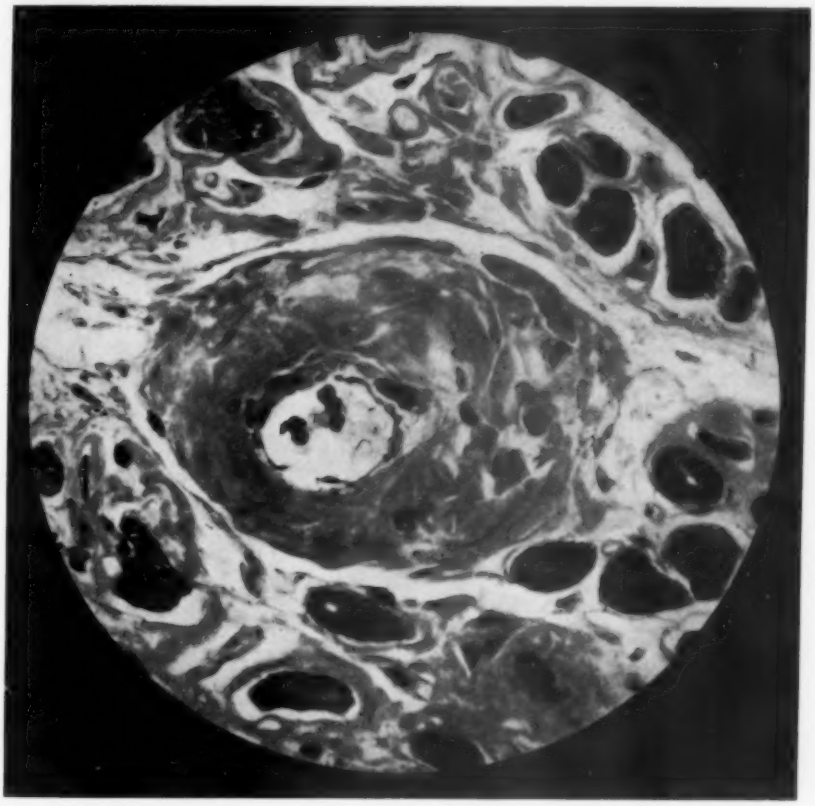

FIG. 2. *Case 1.* A section of myocardium (× 520). A small blood vessel is seen in cross-section. There is heavy sub-intimal deposition of amyloid. This material can also be seen within and around the nearby muscle fibers.

Because of the multiplicity of causes and symptoms, it is difficult to evaluate cardiac failure as the direct cause of death in such a widespread systemic disease as primary amyloidosis. However, the fact that this disease can kill by direct involvement of the heart is known. Kerwin in 1936 [2] described two cases of death due to primary amyloid disease of the heart, and one of his cases closely resembled the above. He also mentioned two reported cases, which seemed to be primary amyloidosis with deaths caused by cardiac disease.[9, 10] Perla and Gross [11] reported another case, a 54-year-old

woman who had chest pain, dyspnea, low blood pressure, and signs of cardiac failure, with sudden death. At autopsy it was found that she had primary amyloid disease of the heart and of other organs. Budd [12] reported a case of amyloid disease of the heart which he called primary, but in which there were no cardiac symptoms. His patient also had carcinoma of the bladder and chronic suppuration of the urinary tract, which cast considerable doubt on the primary or idiopathic aspect of this case.

In Binford's report [4] the patient had cardiac asthma and eventual heart failure, with electrocardiographic evidence of old myocardial infarction. At postmortem examination, it was found that there was stenosing amyloidosis of the coronary vessels and interstitial deposition of hyaline substance in the myocardium, with no associated chronic disease. One of the two cases reported by Pearson [5] was cardiac, but was complicated by the presence of a previously existing hypertension and cardiac failure. Therefore, it cannot be included in this category.

As indicated by our case, primary amyloidosis of the heart may greatly resemble the syndrome of sclerotic coronary artery disease with signs and symptoms of coronary failure and myocardial insufficiency. It holds a position with the other rare but real causes of heart disease, such as arteriovenous aneurysms, nutritional deficiencies, and others described by Weiss.[13] As he points out, the diagnosis in such cases is difficult but can be suspected.

The diagnosis can be made by the signs and symptoms typical of coronary artery disease and myocardial insufficiency in the absence of previously existing hypertension and in the presence of an enlarged liver, spleen, and lymph nodes. This can be confirmed by lymph node biopsy and by a positive Congo red test. It is interesting to note the presence of purpura in this case. Purpura has been previously described by others in primary amyloidosis [5] and is presumably caused by vascular damage due to intercapillary penetration of the amyloid substance.

According to Reimann, Koucky, and Eklund,[7] one of the features of primary amyloidosis is that it reacts weakly, if at all, with the usual differentiating stains. This was not true in this case. The kidneys, liver, spleen, and heart all took the iodine, methyl violet, and Congo red stains very well.

Case 2. C. S., a 57-year-old white housewife, entered the hospital October 29, 1937, and was discharged November 19, 1937. Her chief complaints were constipation for two years, weight loss for one year, and fatigue for seven months. Her family history was irrelevant. She had had rheumatic fever at the age of 10, at which time she was told that her heart was affected. She had mild cystitis three years before admission. This cleared up immediately on treatment, and recurred one year later, when it cleared up permanently with renewal of treatment.

Present illness began 10 months before admission, when she first noted some weakness and weight loss. On routine examination, her physician found an enlarged liver and proteinuria. For the next six months she was kept on a high protein diet, and her tonsils and teeth were removed in the search for foci of infection. During the four months preceding admission, she was treated in the Out-Patient Department of the Peter Bent Brigham Hospital. Here it was noted that her liver was

enlarged; she was slowly losing weight and strength; her urine consistently showed a large trace of protein, with rare casts and white blood cells. On roentgenologic examination the gastrointestinal tract was found to be normal. Intravenous urograms showed a normal urinary tract. Because of these positive findings and the fact that she had lost 35 pounds since the onset of her illness, she was referred into the hospital for further study, with the tentative diagnoses of low grade nephrosis, hepatic enlargement of unknown cause, and possible neoplasm.

On physical examination, the patient appeared to be a well-developed, middle-aged, white woman showing signs of recent weight loss. The vital signs were normal, and the blood pressure was 110 mm. Hg systolic and 76 mm. diastolic. There were ecchymotic areas on the buccal mucous membranes. The lungs were clear to percussion and auscultation. The heart was normal in size, its rhythm was regular, and there was an apical presystolic murmur with accentuation of the first sound. The abdomen was soft. The liver, which was enlarged four fingers' breadth below the right costal margin, was smooth, hard, and tender. Although the spleen was not palpable, the inguinal glands were slightly enlarged. Neurologic, pelvic, and rectal examinations were negative. The ophthalmoscopic examination revealed slight retinal arteriosclerosis.

Laboratory Data. The blood Hinton and Wassermann tests were negative. The urine was concentrated to 1.015, and persistently showed a trace to a large trace of protein, rare, finely granular casts, an occasional white blood cell, and a rare red blood cell. Red cell counts and hemoglobin concentration were normal. The white cell count, which was normal on entry, increased to 33,000 with the terminal fever. The phthalein excretion was 52 per cent in two hours. Studies of the blood chemistry revealed a non-protein nitrogen of 27 mg. per 100 c.c., urea nitrogen of 13 mg. per 100 c.c. The total protein concentration was 5.5 gm. per 100 c.c., with an albumin fraction of 2.6 grams, and a globulin of 2.9 grams per 100 c.c. Fasting gastric analysis revealed 53 units of free acid and 61 of combined acid. The Congo red test was positive, showing 100 per cent withdrawal of the dye from the blood stream in an hour's time. The blood sedimentation rate was 0.2 mm. per minute. Examinations of the stools with guaiac were + to ++++, and terminally they contained bright red blood. Two blood cultures were negative.

Hospital Course. The patient got steadily worse with increasing weakness and emaciation. She had a daily fever around 100° F. until four days before death, when it began to rise steadily to 105° F. For three days before death she passed watery stools which were grossly bloody. Small pinhead-sized petechiae were found in the conjunctivae. Death occurred with hyperpyrexia and cardiac failure.

Clinical Diagnoses. Chronic nephritis, amyloidosis, rheumatic heart disease, possible subacute bacterial endocarditis.

Postmortem Diagnoses. Amyloidosis of the spleen, liver, heart, brain, parathyroid glands, stomach, colon, adrenal glands, and kidneys; bacterial endocarditis of the mitral valves (streptococcus); rheumatic mitral valvulitis, healed; polypoid submucosal hemorrhages of the colon with one area of ulceration; petechiae of the kidneys and small intestine and generalized streptococcus peritonitis; slight atheromatous change in the aorta; fibrosed ovaries.

The heart, which weighed 320 grams, seemed somewhat enlarged and hypertrophied when studied in situ. On dissection, the valves of the right side of the heart were thin, membranous, and freely movable. The mitral valve showed a definite thickening of its leaflets and a distinct nodularity along its free edge. Numerous, small, warty excrescences, which had the appearance of recent vegetations, were situated on the anterior cusps of the mitral valve and on its auricular surface. The aortic valve showed slight thickening, especially along the free edges. There was also a definite thickening of the annulus fibrosus. Microscopic examination of the

mitral valve revealed hyaline thickening of the valve, and polymorphonuclear leukocytes and small bits of fibrin adherent to its frayed surface.

The relationship of primary amyloidosis to rheumatic heart disease and bacterial endocarditis is interesting. In this case the endocarditis was undoubtedly a terminal concomitant. The pathologist's description of the endocarditis was: "There are numerous warty excrescences which have the appearance of recent vegetations." Clinically, the hepatomegaly and proteinuria were noted by her own doctor 10 months before admission. During the six months before admission, while she was being followed in the Out-Patient Department, her temperature was normal and she had none of the signs and symptoms of bacterial endocarditis. It was only a few days before death that petechiae were found, but the blood cultures failed to become positive for streptococci. This patient's initial rheumatic infection occurred 47 years before death.

Amyloid disease occurring secondary to rheumatic fever has been reported by Beattie.[14] He noted four cases in patients under 28 years of age, all having histories of acute rheumatic fever from seven months to several years before death. At postmortem examination two of his cases had bacterial endocarditis, superimposed on their rheumatic valvulitis. In our patient, however, there was no recent recognizable attack of acute rheumatic fever to which the amyloid disease might be secondary. Fishberg[15] mentioned the fact that he has seen these two diseases occurring together, but he did not say whether the amyloidosis was primary or secondary to the bacterial endocarditis.

Case 3. W. K., a 52-year-old plumber, was admitted for the last time on May 24, 1928, and was discharged May 25, 1928. He had had three previous admissions for the same disease. His chief complaints were pain and paralysis of the right leg. His family history was irrelevant. In addition to the usual childhood diseases he had had pneumonia at 25 and gonorrhea at 25 and again at 42.

His present illness began about August 1925, two years and nine months before his last entry, with swelling of the legs and scrotum, most marked at nightfall. He was studied at the Faulkner Hospital in Boston, in November 1925, at which time he was told he had albumin in his urine and should limit his diet and fluids. He did not improve and was admitted to the wards of the Peter Bent Brigham Hospital for the first time in November 1926. At that time he had a marked pallor, anasarca, and ascites. His blood pressure was 145 mm. Hg systolic and 80 mm. diastolic. The blood chemistry was normal. Phthalein excretion was 40 per cent in two hours, and his basal metabolic rate was —20. The urine showed +++ and ++++ albumin with numerous casts. He improved on a high protein diet, with calcium chloride as a diuretic. After discharge he was followed in the Out-Patient Department. His edema gradually reaccumulated. Laboratory data remained unchanged except for his blood pressure, which decreased to less than 120 mm. Hg, and the metabolic rate, which responded with thyroid and rose to —4.

His second admission was in October 1927, at which time he had edema of the hands, lower arms and body from the fifth rib down. An abdominal paracentesis yielded 6,200 c.c. of fluid. Laboratory findings were as before except for the phthalein excretion, which was 65 per cent in two hours. He became free of most of his edema, and was discharged to the Out-Patient Department. Again the edema

reaccumulated rapidly and he was admitted for the third time in December 1927. His edema and ascites were greater than on previous admissions, but responded to tapping and mercurial diuretics, so that on discharge he had lost 10.2 kilograms. The urine now showed albumin, red and white cells, and casts. The stools were benzidine positive. Once more he was followed in the Renal Clinic, and he was maintained on high protein diets and ammonium chloride and ammonium nitrate with salyrgan were administered. Abdominal taps were done when indicated, the last tap, five days before his final entry, yielding 12 quarts of fluid. The serum total protein during this period was 4.94 grams per 100 c.c., with albumin 2.44 grams and globulin 2.50 grams. On the morning of his last admission he awoke to find his right leg tender, more swollen than the left, and very painful and paralyzed.

On physical examination, the patient appeared to be a poorly developed, edematous, chronically ill male, complaining bitterly of pain in his right leg. His temperature was 99.8° F.; the pulse was 110, and respirations were 26. His blood pressure was 85 mm. Hg systolic and 55 mm. diastolic. His eyes, ears, nose, throat, and lungs were normal. The heart was not enlarged; the sounds were regular and of fair quality, without murmurs. The abdomen was slightly distended, symmetrical, with shifting dullness in the flanks and edema of the lower abdominal wall. The arms were normal, but the legs both showed pitting edema, the right more so than the left. The right leg was also warmer, redder, and more tender than the left.

Laboratory Data. The blood Wassermann reaction was negative. The urine concentrated to 1.022 and showed ++++ albumin, numerous hyaline casts, and a few fat droplets. The hemoglobin concentration was 70 per cent (Tallquivst). The red cell count was 3.4 million, and the white cell count 12,000, with 81 per cent polymorphonuclears, 13 per cent lymphocytes, and 6 per cent large mononuclear cells.

Hospital Course. A few hours after entry the pain extended from the right leg to the left leg, the pelvis and back, and was not relieved by morphine. The following morning both legs and the lower abdomen were blue, with a definite line of demarcation at the level of the umbilicus. The patient became comatose and died in respiratory failure.

Clinical Diagnoses. Chronic nephritis with edema (nephrosis); phlebitis of the right leg.

Postmortem Diagnoses. Amyloid and lipoid nephropathy; generalized edema; hydroperitoneum and hydrothorax; amyloidosis of the kidneys, spleen, liver and adrenals; terminal pneumonia; pulmonary congestion and edema; liver necrosis; fibrous pleuritis, left; scars in mesentery.

The kidneys were described as follows:

"Right kidney weighs 295 grams, left 300 grams. The capsule strips with ease. The kidneys themselves are rather soft and somewhat mushy to palpation and are much larger in size than usual. Section through the substance of the kidney shows there is escaping a large amount of fluid. This is apparently clear in color. There is a definite rolling of the margins of the kidney, showing considerable amount of edema. The cut surface of the kidney shows a very striking picture, in that throughout the cortex and medulla and somewhat through the pyramids, there is a diffuse, yellowish, somewhat granular appearance of the kidney tissue. This presumably is chiefly fat, so that in this kidney there apparently is a considerable amount of fatty change within the tubules. Kidneys are somewhat paler in color than is usually found. There is no gross evidence of scarring, either coarse or finely granular in type. The amount of fat in the pelves of the kidneys does not appear to be greatly increased.

"Microscopic examination showed the kidney substance to be edematous. The tubules in many instances are dilated, and in spite of the short time elapsing between death and the postmortem examination (one hour), there is considerable degeneration of the tubular epithelium. Occasional scars are seen in the cortex with connective

tissue increase and inflammatory cell infiltration, which consists largely of lymphocytes. An occasional hyalinized glomerulus is seen. However, the most important lesion seems to be the marked deposit of amyloid along the capillaries in the glomerular tufts and the fatty degeneration in the glomerular epithelium. In addition, there is evidence of acute hyaline degeneration of small blood vessels and capillaries. An occasional cast is seen in the tubular spaces. Several clumps of fat-laden phagocytes are seen."

This case has been presented in the literature before by Christian,[16] primarily as a case of nephrosis due to idiopathic amyloidosis, and as such, has escaped the attention of most writers on amyloidosis. As Christian pointed out, up to that time the nephrotic syndrome was associated only with amyloidosis secondary to chronic suppuration, tuberculosis, syphilis, and certain neoplasms, and the occurrence of nephrosis and primary amyloidosis was not recognized. Dr. Christian also suggested that the amyloidosis in this case may have been the result of the treatment of the nephrosis with high protein diets and thyroid.

The duration of symptoms in this patient was three years, which is slightly longer than the usual average of two and a half years for primary amyloidosis. According to Fishberg,[15] most patients who develop secondary amyloidosis of the kidney die within six months to a year.

The diagnosis of primary amyloidosis of the kidney is important, since patients with nephrosis may recover, whereas those with extensive primary amyloid disease probably never do. There are reports of recoveries in secondary amyloid disease when the causes of the amyloidosis are cured or removed, but we have been unable to find any mention in the literature of cures and recoveries in the primary disease.

Summary

Out of 120,785 admissions and 41,551 autopsies, there were 23 cases of proved amyloid disease, of which only three were found to be primary. One of these simulated sclerotic coronary artery disease with heart failure, a second terminated in subacute bacterial endocarditis, and the third gave the clinical picture of the nephrotic syndrome.

Although the diagnosis of primary amyloidosis is difficult, it should be suspected for prognostic reasons.

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CASE REPORTS

THROMBOSIS OF THE AXILLARY VEIN *

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The literature on the subject of thrombosis of the axillary vein is rather scant. The first description of this as a clinical entity was made in 1884 by Von Schrotter [1] who expressed the opinion that thrombosis of the axillary vein followed an effort which resulted in a sudden stretching of the vein and compression of its walls. The damage thus produced in the vessel wall resulted in a localized phlebitis. In 1920, Cadenat [2] reviewed the literature and collected 27 reported cases. Gould and Patey [3] added eight cases of their own in 1928. Paggi [4] in a review in 1933 was able to collect 74 cases for study. One year later Matas [5] added his case and summarized 100 cases which had been reported.

Case Report

A 20-year-old female was taken ill with an upper respiratory tract infection six weeks before she came under observation. This lasted about one month during which time she had a non-productive cough but had no elevation of temperature. Two weeks before admission, she noticed that her right upper extremity appeared swollen and was heavier than the left. The swelling gradually increased. At no time during the six week period did she complain of pain or have any discomfort aside from the fact that she could not fit her right arm into a dress and noticed that her skin was "becoming tense."

Table I

Measurements Obtained at Various Levels on Two Occasions

	1/22/38		2/15/38	
	Right	Left	Right	Left
Just below axilla	28 cm.	25¾ cm.	30 cm.	26 cm.
Above elbow	24½ cm.	22 cm.	23.2 cm.	21.5 cm.
Below elbow	23½ cm.	22 cm.	24.0 cm.	22.0 cm.
Wrist			15.5 cm.	15.0 cm.

Her family history was non-contributory. The past history was significant in that three years before coming under our observation, while partaking in a track meet, the patient ran into a stone wall, crashing her right elbow and shoulder against the wall. The arm became swollen and painful within a few hours. She was taken to a hospital where the arm was immobilized in flexion for three days. The swelling and pain gradually subsided, and after several days she made a complete recovery.

At the age of 11 the patient had had rheumatic fever which left no sequelae.

Examination revealed a well developed and well nourished white female lying in bed in no apparent distress. The right upper extremity had a purple reddish hue.

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There was fullness in the right infraclavicular region extending toward the head of the humerus. The remainder of the arm was swollen from the axilla to the tips of the fingers. The natural folds of the skin of the forearm were obliterated. The skin was tense, but did not pit on pressure. There was no limitation of the range of motion of the arm. The radial pulse was palpable but the transmitted impulse was slightly diminished. Veins were visible extending from the right sternoclavicular junction to the forearm. The axillary lymph nodes were not enlarged. The arterial filling time was the same on both sides. The pertinent negative findings were absence of a "Horner's collar," no tracheal tug or fixation, no broadening of the mediastinum, absence of tenderness above the right clavicle, and absence of a cervical rib. The remainder of the physical examination was entirely normal.

Comparative measurements of corresponding levels of the two arms are shown in table 1.

Laboratory data: hemoglobin 81 per cent; red blood cells 4,010,000; white blood cells 13,050; polymorphonuclear neutrophiles 90 per cent, lymphocytes 7 per cent, eosinophiles 1 per cent; basophiles 2 per cent. The Wassermann and Kline tests were negative. Urinalysis was normal. Urea nitrogen was 11.5 mg. per cent. The red cell sedimentation rate was within normal limits on three occasions. Bronchoscopy failed to reveal the presence of intrinsic or extrinsic lesions in any of the bronchi. There was no evidence of paralysis of the vocal cords. In order to study the effects of obstruction to the venous flow on the products of metabolism, tests were carried out as recorded in table 2.

TABLE II

Comparison of Products of Metabolism in the Blood of Both Arms

	Right	Left
Oxygen content of blood (venous)	12.3 vol. per cent	14.8 vol. per cent
Sugar	97 mg. per cent	97 mg. per cent
Carbon dioxide combining power	64.4 vol. per cent	66.3 vol. per cent
Circulation time	10.2 sec.	8.2 sec.
Venous pressure	24.5 cm. blood	12.0 cm. blood

Studies of the venous oxygen content, sugar, and carbon dioxide combining power were made on the blood obtained from each arm and the circulation time and venous pressure were determined. The blood sugar was the same in the blood of both arms. The oxygen content and the carbon dioxide combining power were slightly lower in the blood of the left arm. The circulation time (calcium method) was slightly prolonged on the right side, and the venous pressure although increased in both arms, was twice as high on the right side as it was on the left side. Roentgen-ray examination of the heart, lungs, esophagus and both shoulder regions failed to reveal the presence of any abnormality in size, shape, or position of these structures.

A study of the venous structures (figures 1 and 2) of the right arm by means of a contrast substance injected into the median basilic vein at the elbow revealed a pronounced tortuosity of one of the arm vessels which passes up to the shoulder. No contrast substance could be seen entering the subclavian vein.

A diagnosis of thrombosis of the right axillary vein was made. During the course of her hospital stay, the patient was afebrile. She remained under observation about five months. By the end of this time, the right upper extremity had returned to its normal size. There was a free range of motion of the entire arm. The veins which were prominent on admission were noted to persist until the patient was discharged.

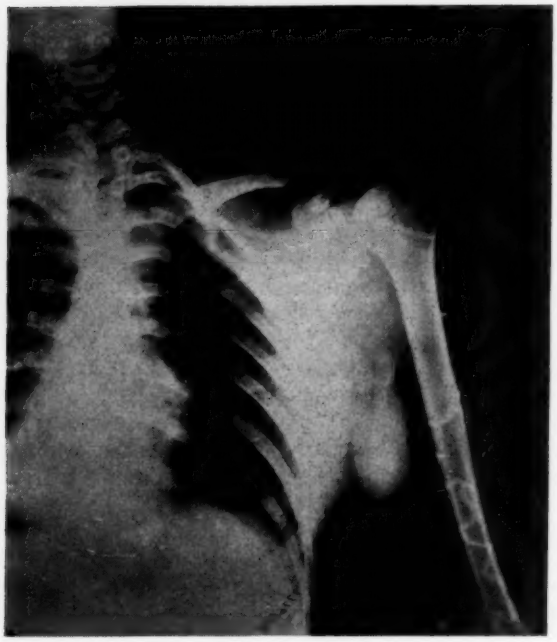

FIG. 1. Contrast substance injected into the median basilic vein at the elbow. Note the pronounced tortuosity of one of the vessels of the arm which passes to the shoulder.

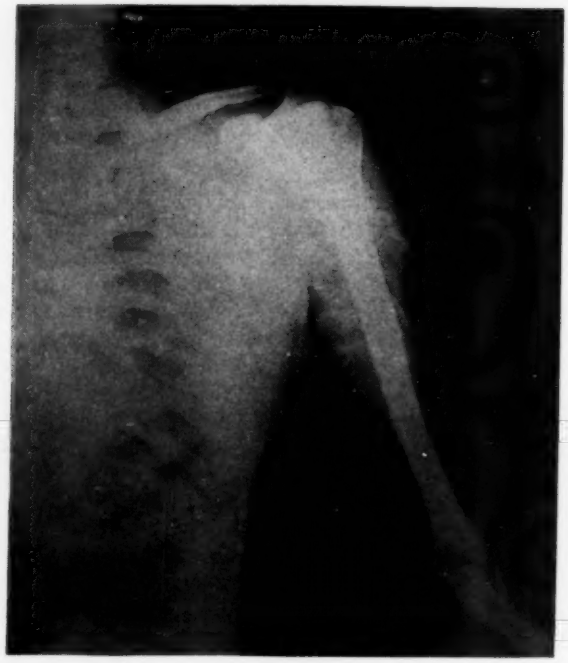

FIG. 2. No contrast substance could be seen entering the subclavian vein.

Anatomy. The axillary vein is of large size and is the continuation upward of the basilic vein. It commences at the lower border of the tendon of the teres major muscle, increases in size as it ascends by receiving tributaries corresponding to the branches of the axillary artery and terminates immediately beneath the clavicle at the outer border of the first rib, where it becomes the subclavian vein. It is covered in front by the pectoral muscle and the costocoracoid ligament and lies on the thoracic side of the axillary artery. Near the lower margin of the subscapularis muscle, it receives the venae comites of the brachial artery and near its termination, the cephalic vein. This vein is occasionally connected with the external jugular or subclavian veins by a branch which passes from it upward in front of the clavicle. The vein is provided with a pair of valves opposite the lower border of the subscapularis muscle. Valves are also found at the termination of the cephalic and subscapular veins. Other tributaries are the long thoracic vein and the costoaxillary veins which come from the first six intercostal spaces and convey the blood from the intercostal veins to the axillary.

Etiology and Pathology. The lack of autopsy material has proved a distinct handicap in determining the pathogenesis of this disease. Many theories attempting to explain the etiology of the thrombus have been advanced. Some of them will be reviewed briefly. The history suggests that trauma of some type is responsible for the thrombosis of the axillary vein, and most authors are agreed as to the significance of trauma in the production of this condition. Lowenstein [6] apparently made the first serious attempt to study the anatomic structures in the axillary area with reference to this problem. By means of a series of anatomic dissections of 37 cadavers, he found that with the arm in the abducted position the costocoracoid ligament, together with the subclavius muscle, made an indentation in the axillary vein. He concluded that these structures were responsible for trauma to the distended vein when the arm was in marked abduction or extension during muscular effort. Venous stasis or circulatory slowing is produced by the forced expiration that accompanies effort. Under these circumstances, pressure on the vein by the costocoracoid ligament and by the subclavius muscle could be sufficient to effect changes in the vascular endothelium capable of producing thrombosis of the axillary vein.

Gould and Patey [3] confirmed this observation by injecting plaster of paris into the axillary veins of cadavers, with the arm flexed in the abducted position; they found, in one subject, that there was a definite groove in the axillary vein corresponding to the course of the costocoracoid ligament. In two other cases they observed a broad, deep groove which had been produced by the subclavius muscle. They demonstrated a competent bicuspid valve in this area. These observers were of the opinion that the subclavius muscle was responsible for the trauma to the vein and resulted in rupture of the valve at the junction of the subclavian and axillary veins, and that this was the fundamental pathologic basis for the formation of the thrombus. Most authors [7, 8, 9] agree that trauma was the etiologic factor in axillary thrombosis. The mode of onset, its predilection for young healthy men and the involvement of the right arm are in favor of this theory.

On the basis of roentgenographic and autopsy studies, Veal and McFetridge [10] reported that the constriction of the vein occurred not as was previously believed over the first rib beneath the subclavius muscle but below the head of the humerus and against the subscapularis muscle. Stretching of the vein

takes place within that part of the vein proximal to the point of constriction below the head of the humerus. Although these facts may be true of cases with marked trauma, it still does not explain the cases in which the accidents are too trivial or those rare spontaneous cases without history of injury.[11, 12, 13]

According to Matas [5] infection cannot be considered as a constant basis for the thrombosis. He cited 27 cases in which the thrombus was removed; in seven of these the material was subjected to culture. In four cases the cultures were sterile; in the other three cases one yielded *Streptococcus viridans*, the second, *Staphylococcus albus* and colon bacillus, and the third, streptococcus. Changes in the vessel wall were also present, indicating a severe inflammatory type of septic phlebitis. The clinical history, the absence of a rise in temperature and the absence of other evidences of toxemia in many cases spoke against an infectious etiology of this entity.

Syphilis, though often mentioned and suggested as a causative factor, was stated by Lowenstein [6] to be "as rare as syphilitic arteritis is common."

Taylor,[14] in describing a case of primary thrombosis of the subclavian vein, was of the opinion that an idiosyncrasy in size or position of some anatomical structure, such as bone, ligament or muscle, might be a predisposing factor in all cases of thrombosis from effort. He held that the axillary vein was not subject to pressure, but that thrombosis in the axillary vein might have its origin in the subclavian vein which with the artery, could be compressed by certain movements involving much play at the shoulder girdle, as, for instance, in rowing.

Diagnosis

Reviewing the cases of various authors, one finds that the patients were young, robust, muscular individuals, engaged in heavy work, and that males were affected as in the cases reported by Rosenthal,[15] Cadenat,[2] Finkelstein,[16] Winterstein,[17] Clute,[18] and others. The right arm was more often involved than the left. Those whose left arm was involved either were left handed, had thrown an unusual strain on the arm,[19] or had sustained an injury to the left side of the chest.[20]

The diagnosis is based on the following factors: There is usually a history of an accident or an injury by strain although occasionally it may develop spontaneously. Swelling of the arm occurs immediately or several hours or days after the sudden muscle strain or repeated muscular effort. The swelling spreads over the entire arm without any rise in body or local temperature, and without local inflammatory symptoms or any constitutional reaction. The skin has a cyanotic hue. Venous collaterals develop on the affected arm and over the anterior part of the chest. A tender cord is present in the axilla, although this is not a constant finding. Venous pressure in the veins of the affected arm is increased. The venous oxygen content on the affected arm is lowered.[17] The blood flow from the basilic vein on the affected side is increased as compared with the normal side.[11] The blood pressure and oscillometer readings in the affected arm may vary slightly from the opposite arm by showing either a slight increase or a diminution. Visualization of the veins with opaque medium reveals the presence of numerous collaterals, distended venous valves, and stasis of the dye in the vessels. Infra-red photography visualizes numerous superficial veins in the affected arm, axilla, and over the chest.

Prognosis

The prognosis as to life is good. The duration of the disability varies from a few months to a year or more because of the persistence of edema. Recurrences have been reported. The rarity with which embolization occurs in axillary vein thrombosis is indicated by the fact that Matas [5] reported but one case of pulmonary embolism in his excellent review of the literature. This occurred in a 70 year old woman who sustained a fracture of the neck of the humerus. The pulmonary embolus was found at autopsy. Relapse is often provoked by the same sort of effort which was responsible for the initial attack. Patients should always be advised against performing the same type of motion.

Treatment

Thrombosis of the axillary vein is best treated by complete rest, elevation of the extremity, and local application of heat. Rest and elevation should be maintained until the edema has subsided and an adequate collateral circulation has developed. Resumption of activity should then be gradual. Veal [21] does not feel that the results obtained following surgical intervention have justified further attempts to relieve the acute symptoms.

Summary

A case of idiopathic axillary vein thrombosis with recovery is reported.

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A CASE OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD WITH INTERESTING HEREDITARY FEATURES *

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ON January 27, 1938, a man, aged 24, was brought to the Neurological Institute of New York, apparently moribund, suffering with subacute combined degeneration of the spinal cord secondary to pernicious anemia. His mother and paternal uncle had had the same disease. This hereditary background, the abnormally early onset of the illness, and the unusually good response to therapy have prompted the presentation of this case report.

Hurst,[1] Meulengracht,[2] Johannessohn,[3] Tscherning,[4] Ungley and Suzman,[5] and others have presented instances of subacute combined degeneration occurring in more than one member of a family. Wilkinson and Brockbank [6] in 1931 reviewed the literature, collecting (1) 125 families in which two or more members were affected with pernicious anemia with or without the complication of subacute combined degeneration of the spinal cord; (2) 51 families in which pernicious anemia and achlorhydria existed simultaneously; and (3) 14 families in which achlorhydria was found without pernicious anemia. They added to the first group 14 cases from their own material; to the second group 8; and to the third group 3.

CASE REPORT

D. C., a 24-year-old white male, employed as a clerk, was admitted to the Neurological Institute of New York January 27, 1938. He had had Sydenham's chorea at age 12, after which he was told that his heart had been damaged. During the last eight months of 1935, at the age of 22, he lost a total of 48 pounds of body weight, was easily fatigued, and noticed progressive muscular weakness and palpitation of the heart. Vomiting and extreme weakness of three days' duration necessitated his hospitalization in Brooklyn January 29, 1936. His skin was then pale lemon yellow, the cardiac apex was outside the midclavicular line, and a double murmur was audible over the mitral area. The heart rhythm was regular. The liver and spleen were not palpable. There were 2,000,000 erythrocytes per cu. mm. of blood, with moderate poikilocytosis and

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From the Neurological Institute of New York, New York City.

anisocytosis. The hemoglobin was 60 per cent (method not stated) and the color index 1.5. The leukocyte count was 7,250 per cu. mm., of which 75 per cent were polymorphonuclear neutrophiles, 3 per cent eosinophiles, 1 per cent basophiles, 20 per cent small lymphocytes, and 1 per cent monocytes. No gastric analysis was done. A diagnosis of pernicious anemia was made, and the patient was given "Jeculin" (a proprietary liver and iron preparation), 4 c.c. by mouth three times daily, and an iron preparation by hypodermic (exact preparation and dosage not known).

He gained weight, but never felt really well. After January 1937 he was weak and lethargic, and his tongue was often sore. There were occasional episodes of palpitation of the heart. In September 1937 he noticed numbness and tingling in the toes of both feet. Marked weakness of both legs set in. Intermittent spontaneous jerking motions of both legs began November 1937, accompanied by unsteady gait and urinary frequency with urgency, nocturia, and occasional dribbling incontinence. He became bedridden and was hospitalized in Brooklyn December 27, 1937. His blood then contained 4,010,000 erythrocytes per cu. mm., with hemoglobin 76 per cent (method not stated); the color index was .95. There were 6,900 white blood cells per cu. mm., of which 72 per cent were polymorphonuclear neutrophiles and 28 per cent large lymphocytes. Other laboratory tests, including examination of the spinal fluid, were normal, but no gastric analysis was performed. No definite diagnosis was made. The only antianemic medication continued to be "Jeculin" by mouth and an unspecified type of iron preparation parenterally. The patient became rapidly more ill. About January 24, 1938, he became disoriented and refused food, fluids, and medications. He was transferred to the Neurological Institute of New York January 27, 1938.

On admission there he was disoriented and negativistic, hallucinated actively, and expressed ideas of persecution. His skin was pallid and subicteric. He was mildly emaciated and markedly dehydrated. His temperature was 101.4° F. rectally, blood pressure 130 mm. Hg systolic and 70 mm. diastolic, and pulse 122. The tongue was smooth and raw at its edges and tip, but not atrophic over the dorsum. The cardiac apex was in the sixth interspace 2 cm. beyond the midclavicular line. There were presystolic and systolic murmurs at the apex, transmitted into the left axilla. The rhythm was regular. There were no basal lung râles and no ankle edema. The liver and spleen were not palpable. From an area of inguinal intertrigo numerous superficial pustules had been seeded over both legs, buttocks, and forearms. At no time was he observed to move either leg at all. Both arms were moved equally well, but weakly. His legs were markedly spastic, his arms mildly so. There was marked bilateral hyperreflexia, with patellar and ankle clonus and Babinski and Hoffmann responses. Sensory examination was impossible.

His blood on admission contained 3,160,000 erythrocytes per cu. mm., showing marked macrocytosis, poikilocytosis, and some polychromatophilia. The hemoglobin was 78 per cent Sahli and the color index 1.26. There were 11,400 leukocytes per cu. mm., of which 72 per cent were polymorphonuclear neutrophiles and 28 per cent lymphocytes. The urine showed a faint trace of albumin and occasional pus cells, but was otherwise negative. The erythrocyte sedimentation rate was 107 mm. in one hour. The blood urea nitrogen was 18 mg. per 100 c.c., and the blood sugar, fasting, 93 mg. per 100 c.c. The cerebrospinal fluid contained 163 red blood cells (the result of trauma) and 3 white blood cells per cu. mm., and 38 mg. of protein per 100 c.c. The spinal fluid Wassermann reaction was negative in all dilutions, and the colloidal gold curve was normal. The manometric response to jugular compression was normal. Gastric analysis, done on two occasions, both with histamine, showed no free acid in any specimen. Blood Wassermann reaction, blood cultures, blood agglutinations for typhoid, paratyphoid, and Brucella, as well as roentgen-rays of the spine, skull, sinuses, and teeth, were negative. The electrocardiogram showed no important findings.

High-caloric, high-vitamin tube feedings with added ground liver were necessary twice daily during the first week. The patient received Lederle's concentrated liver extract, 3 c.c. intramuscularly, daily, and thiamin chloride 10 mg. by hypodermic daily for the first 50 days. Thereafter, he received Lederle's concentrated liver extract 3 c.c. intramuscularly three times weekly, with thiamin chloride, 8 mg. by mouth daily. In addition, he received ventriculin 10 gm. three times daily from February 25 until he was discharged April 5. Dilute hydrochloric acid was given with meals. Care of the skin was stressed. He was given daily massage to the legs and arms, together with passive, and later, active exercises. Reëducational walking exercises were instituted at the earliest possible time, 21 days after admission, and were continued until discharge.

After an initial 10 day period of fever ranging as high as 103° F., the patient was fever free. Psychotic symptoms disappeared eight days after admission; he became coöperative and rational, but, in marked contrast to his previous shy, withdrawing personality, he was loud, rambling, and discursive in speech, and forward in manner. Seven days after admission, and one day before cessation of psychotic symptoms, there was a reticulocyte response of 13.8 per cent; the erythrocyte count on that day was 2,840,000 and the hemoglobin 72 per cent Sahli. Nine days after admission the reticulocyte count was still 13.4 per cent; the erythrocyte count had risen to 3,220,000 and the hemoglobin to 78 per cent. Subsequently the blood picture improved steadily. The reticulocyte count remained as high as 12.6 per cent until 13 days after admission and was still 5.4 per cent 32 days after admission, when the erythrocyte count had reached 4,240,000 and the hemoglobin was 90 per cent Sahli. Forty-three days after admission the erythrocyte count had attained 5,040,000, and the hemoglobin 102 per cent Sahli. On discharge from the hospital April 5, 1938, the erythrocyte count was 5,180,000 and the hemoglobin 104 per cent Sahli. Interestingly, the leukocyte count averaged about 12,000 until the patient's discharge, although he was afebrile and all evidences of infection had been eradicated.

Eight days after admission and one day after the onset of marked reticulocyte response, incontinence of urine and feces practically ceased, and the patient began to exhibit slight muscular power in both legs, especially in the proximal musculature. Sensory examination, now possible for the first time, found no impairment of sensibility to painful or tactile stimulation, but vibratory and position sense were lost in both legs. Motor power now improved rapidly. Twenty-two days after admission it was estimated as being 50 per cent for all motions of the legs and 100 per cent for all motions of the arms. Walking exercises were instituted on the twenty-first day. Thirty-seven days after admission muscular power was assessed as normal for all motions tested, in all extremities. Thirty-nine days after admission the patient was able to walk the length of the gymnasium, on a rubber mat, supported by a cane; the gait was clumsy, spastic, and ataxic. Fifty-four days after admission the patient was able to walk short distances without a cane, with little spasticity or ataxia. On discharge from the hospital April 9, 1938, 72 days after admission, he was able to walk the length of the ward without his cane.

When the patient was reëxamined at the time of his discharge, none of the extremities showed more than slight spasticity. He fell in the Romberg position with the eyes closed, and swayed moderately in the same position with the eyes open. The heel-to-knee test was performed in a mildly ataxic manner on both sides, but the finger-to-nose tests were well done. Vibratory and position sense were still absent in both legs. Marked hyperreflexia continued, with transient patellar and ankle clonus, and Babinski responses. The rest of the systemic examination remained essentially unchanged, save for complete elimination of furunculosis and marked improvement in general well-being.

Treatment was continued in the hematology outpatient department, where the patient received intramuscular injections of Lilly's liver extract, 6 c.c. weekly. He continued to take dilute hydrochloric acid by mouth, and 300 International units of thiamin chloride by mouth daily. May 18, 1938, less than four months after his admission to Neurological Institute, he had discarded his cane and was able to walk as much as 14 blocks at one time. He was still very unsteady in the Romberg position. He returned to his former clerical job, which he has continued to fill adequately. His blood count was maintained above 5,000,000 at all times. On April 19, 1939, there were 5,600,000 erythrocytes per cu. mm., with hemoglobin 17.5 gm. The leukocyte count was then 8,550 per cu. mm., with 69 per cent neutrophiles, 4 per cent eosinophiles, 20 per cent lymphocytes, and 7 per cent monocytes.

When reëxamined January 14, 1939, one year after his admission to Neurological Institute, the patient was mentally clear, but still garrulous and discursive. He was florid, somewhat obese, and in obvious good health. He said he was able to walk well without a cane, even on an icy street, and noticed only that he was unable to run. Gait was adroit and confident, with minimal spasticity and tendency to overadduction of either leg as it was moved forward in walking. The Romberg was negative; heel-to-knee and finger-to-nose tests were well performed. Hyperreflexia, clonus, and Hoffmann and Babinski responses were still present bilaterally. Position sense was still absent in all the toes, and vibratory sensibility was absent in the hips, sacrum, and legs.

He was seen again May 24, 1939, approximately 16 months after he had been admitted to Neurological Institute. His functional improvement had been maintained. Gait was excellent. Exaggerated deep reflexes, with transient clonus, continued. There was possibly slight restoration of position and vibratory sensibility in the right foot.

Discussion of Hereditary Background. The patient's father was of "Scotch-Irish" descent, the mother of Swedish stock. The mother and one paternal uncle had pernicious anemia with subacute combined degeneration of the spinal cord. A search through three generations of both families located no other cases of anemia or locomotor difficulty. The paternal family is now resident in Alberta, Canada, and could not be examined. The maternal sibling group (five in all) lives in Brooklyn. They permitted the performance of blood counts, but would not submit to gastric analysis. The lowest erythrocyte count was 4,780,000 per cu. mm. The lowest hemoglobin was 82 per cent. The stained blood smears showed no significant variation from normal. The patient's only sibling, an older sister, aged 26, submitted to both blood count and gastric analysis. The former showed an erythrocyte count of 4,800,000 with hemoglobin 88 per cent Sahli, and color index of .91. There were 11,700 leukocytes per cu. mm. The fractional gastric analysis (histamine method) showed large amounts of free hydrochloric acid in each specimen, the maximum being 120 degrees at the end of 30 minutes.

At the age of 41 (in 1930) the patient's mother had developed rapid, progressive anemia, with paralysis of both legs, and died within six weeks of the onset of symptoms. Unfortunately little more is known of the history of her case. When she was admitted to the Hackensack Hospital, Hackensack, New Jersey, her blood count showed 1,150,000 red blood cells per cu. mm., with hemoglobin 20–25 per cent (method not stated). The white blood cells numbered 8,600 per cu. mm. The urine showed one plus albumin and occasional

white blood cells, but was otherwise negative. The blood Wassermann reaction was 4 plus. The autopsy diagnosis was pernicious anemia.

A paternal uncle at the age of 44 began to tire easily, and noticed that his skin was yellow in color. A few months later there set in throbbing midlumbar pain, and soon thereafter lower abdominal numbness with progressive loss of power of the legs, and ataxia. He was admitted to the University of Alberta Hospital * July 16, 1934. Examination at that time showed marked pallor, with icterus. The patient was irritable and somewhat facetious. Otherwise the general systemic examination was negative. There was weakness of both legs

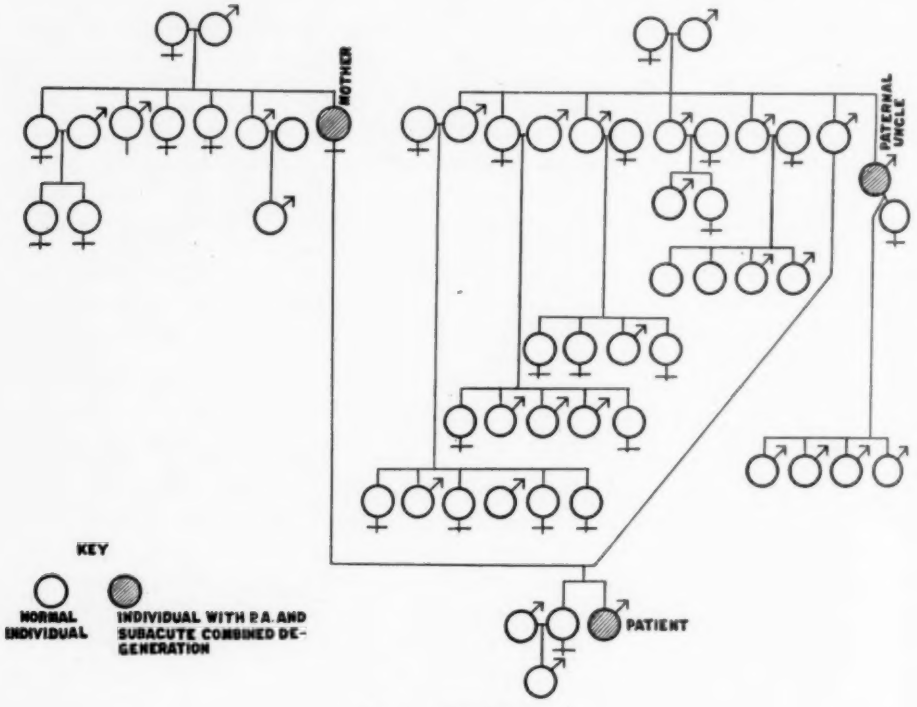

FIG. 1. Family tree.

with spasticity. Strength in the arms was normal. Ataxia was present in arms and legs. Vibratory sensibility was impaired in both legs. The position sense was apparently not tested. The deep reflexes were exaggerated throughout, with bilateral ankle and patellar clonus. There was a bilateral Babinski response. The blood count at that time showed 2,280,000 red blood cells with 8.5 gm. hemoglobin and color index 1.3. There was poikilocytosis, anisocytosis, and macrocytosis. There were 3,100 white blood cells per cu. mm. The blood Wassermann reaction was negative. Gastric analysis showed no free acid in any specimen. Spinal fluid examination was negative. The patient was placed on liver therapy (exact details not known). We do not know his subsequent blood counts, but he is said to have improved markedly and to be able to walk at present with the aid of two canes.

* To which we are grateful for the following report.

Discussion

It is unusual, but not entirely unheard of, for pernicious anemia to set in so early in life. Fortunately, such marked progression of symptoms in these days is very rare, because adequate liver therapy (i.e., liver by intramuscular injection) is usually initiated early in the course of the illness. This patient received nothing but oral liver preparations until he was practically moribund. This case again emphasizes the advisability of maintaining the blood count at 5,000,000 or above in order to make less likely the occurrence of neural symptoms. Subsequent to the initial diagnosis of pernicious anemia this patient's blood count was elevated in an apparently satisfactory manner. Neural symptomatology advanced rapidly while the red blood cell count was as high as 4,010,000 with hemoglobin of 76 per cent (December 1937). This case also belies the pessimistic teaching maintained by many that one can hope only for arrest of neural symptoms, but not for any substantial return to normal, despite therapy. Attention is called to the massive parenteral liver therapy employed in this case and to the administration of thiamin chloride parenterally; further, to the early and vigorous employment of physiotherapeutic measures; i.e., massage and passive exercise, followed as soon as possible by active exercises and later by reëducational walking exercises. It was interesting that psychotic symptoms were substantially cleared before any rise in red blood cell count occurred, but one day after a substantial reticulocyte response took place (13.4 per cent).

Pernicious anemia, with subacute combined degeneration of the spinal cord, was present in one member each of the preceding generation in both the maternal and paternal families. The patient's only sibling was free of any of the stigmata of pernicious anemia, including achlorhydria. Pernicious anemia occurred after the age of 40 in both of the affected members of the preceding generation, but in the patient it occurred in the early twenties. Although only three cases are involved, there is a suggestion that the illness tends to occur at earlier ages in successive generations. This tendency was also evident in the family reported by Ungley and Suzman.[5] The scanty data here presented suggest hereditary transmission of the disease as a Mendelian recessive character.

Summary

A young man developed pernicious anemia at the age of 22 years and subacute combined degeneration of the spinal cord at the age of 24, after inadequate, purely oral, liver therapy. Both his mother and a paternal uncle had had pernicious anemia and subacute combined degeneration. The familial background is presented in some detail. The patient entered the hospital moribund, completely paralyzed in both legs, and psychotic. He was placed under intensive therapy, which included massive doses of intramuscular liver and parenteral thiamin chloride, followed by massage, passive and active exercises, and as soon as at all practicable, reëducational walking exercises. Fifty-four days after admission the patient had attained the ability to walk short distances, unsupported, even with a cane. Four months after admission he had returned to work and had improved to the point of discarding his cane entirely, walking as much as 14 blocks at one time. This improvement has been maintained. When the patient was last seen, 16 months after admission to the hospital, gait

was for all practical purposes normal. Hyperreflexia, pathological reflexes, and impairment of vibratory and position sense in the legs persisted. It is suggested that this remarkable improvement was due to the employment of doses of intramuscular liver much larger than ordinarily used, and maintained over a long period of time, to the employment of substantial doses of parenteral thiamin chloride, and the early initiation of vigorous physiotherapeutic and reëducational measures. Continued improvement, without relapses, following the patient's discharge from the hospital was greatly aided, we believe, by maintenance of the patient's blood count above 5,000,000 red blood cells per cu. mm. with appropriate doses of intramuscular liver. Pernicious anemia and subacute combined degeneration may have an hereditary basis, with transmission after the manner of a Mendelian recessive character. The disease may have a tendency to occur at progressively earlier ages in successive generations.

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FRIEDREICH'S ATAXIA *

By A. C. Woofter, M.D., F.A.C.P., and B. S. Parks,† M.D.,
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In 1861 Nicolaus Friedreich first described a primary hereditary spinal cord disease which caused progressive ataxia of first the legs and then the arms, but without paralysis of the sphincters or disturbance of the senses. He correctly assigned the major pathologic lesions to the region of the posterior and lateral columns, designating it a chronic degenerative atrophy, but thought it closely related to tabes dorsalis, a belief which was later disproved. Following this several similar cases were reported and later many variations from the usual type were described, such as those in which cerebellar involvement predominated, a form now classed as Marie's cerebellar ataxia.

Friedreich's ataxia is one of the many unusual neurological diseases that are both rare and interesting. Characteristically it has its onset early in life, between the ages of five and 14, although in one family reported (Brown) the

* Received for publication October 23, 1937.
† Deceased.

youngest member was six and the oldest 39 when the earliest manifestation of the disease appeared. Jenrassik has reported a case beginning in a patient 50 years old.[10]

The syndrome progresses slowly and relentlessly without regard to treatment. There are frequently long remissions, however, and the patient may reach old age.[10]

The affected individual has, so far as can be told, an inherent neurone deficiency with a tendency to specific central nervous system degeneration passed

FIG. 1.

on by some previous generation, although a definite family history is by no means invariably found.

There are many causes for pathologic changes involving the posterior and lateral columns of the spinal cord simultaneously. Pernicious anemia, leukemia, aplastic anemia, diabetes, pellagra, syphilis, and chronic ergot poisoning are among the more common types. However, these are owing to diseases not primary in the central nervous system; none of them is known to produce any deformity of the feet, and their differentiation from this disease is usually easy.

Amyotrophic lateral sclerosis, according to Boyd, may cause pes cavus, but there should be little cause for difficulty in differential diagnosis. The onset of amyotrophic lateral sclerosis is in the upper extremities with atrophy of the

thenar and hypothenar eminences, progressing up the arms toward the shoulders but often leaving intact some muscle groups.

The first symptom, stumbling while running or walking, apparently is owing to the progressive onset in the proprioceptive fibers of Goll and Burdach (posterior columns). These columns carry no pain fibers and thus involvement accounts for the presence of some of the characteristic manifestations of tabes

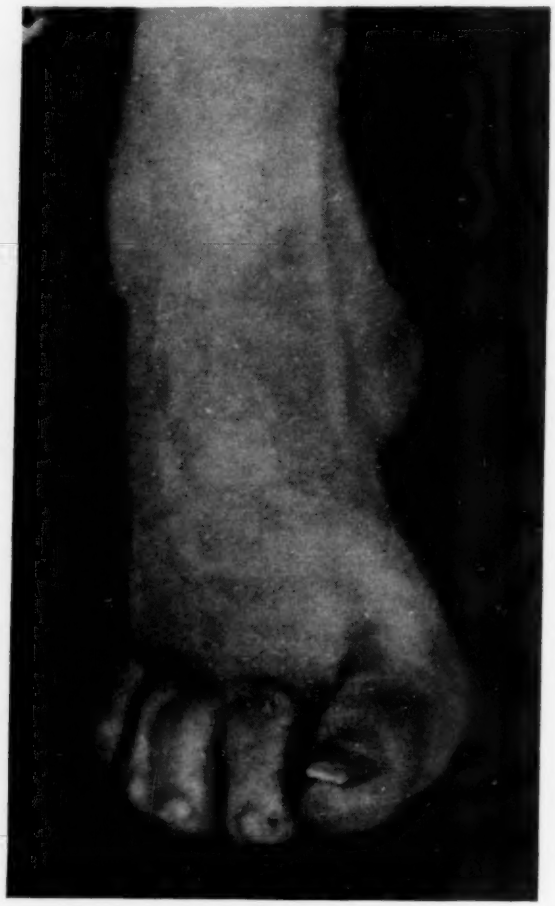

FIG. 2. Anterior view of the right foot illustrating the continuous Babinski position of the toes.

dorsalis, namely a positive Romberg sign, and loss of sense of motion and position of the great toes. However, this disease can be differentiated from locomotor ataxia by the absence of tabetic crises, Argyle-Robertson pupils, girdle sensations, by absence of the characteristic serologic changes in the blood and spinal fluid, and by the difference in gait.

To the involvement of the lateral columns is attributed the characteristic

bilateral deformities of the feet with occasional fixation of one or both ankle joints. There is a pes cavus accompanied by a "continuous Babinski sign" with persistent extension of the great toes and plantar flexion of the remaining digits. This makes it impossible to make the usual tests for the presence of abnormal extensor reflexes.

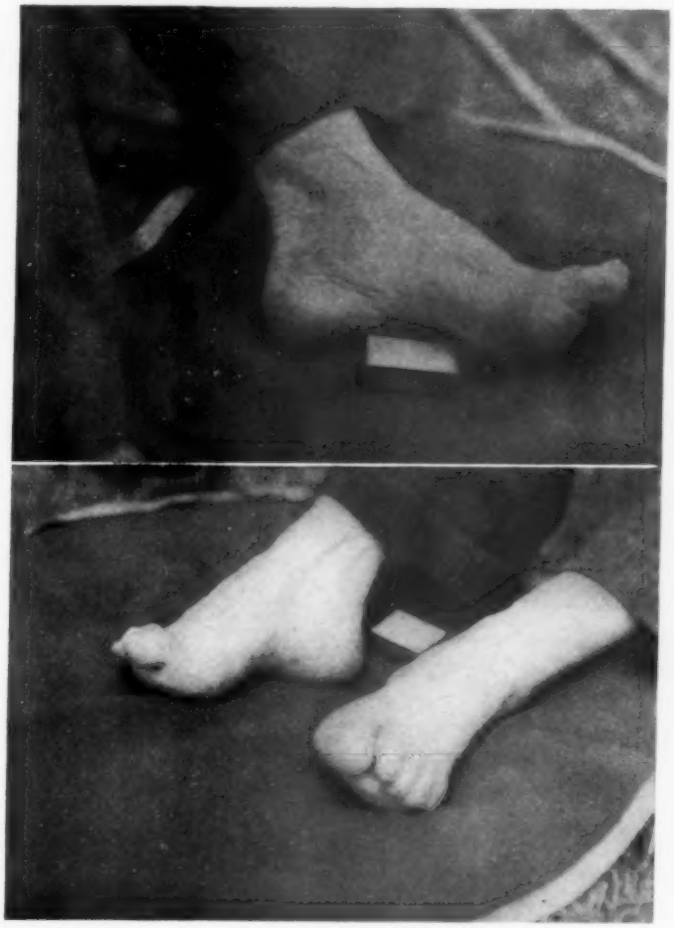

FIG. 3 (above). Lateral view of the left foot showing extension of the great toe and moderately well the pes cavus. (below) Lateral view of the right foot showing the pes cavus.

Late in the course of the disease there is sometimes a loss of the knee jerks owing to degeneration of fibers proximal to the sensory ganglia.

In most cases the direct cerebellar tract is invaded with the production in varying degree of vertigo, increased ataxia, and a "drunken reel" in the gait. A gross tremor of the upper extremities and head is always present.

There is no pain, and there is no disturbance of superficial pain, temperature, or touch sensations. The mentality remains approximately normal, although this is occasionally disturbed in the terminal stages.

Macroscopically the greatest pathologic change is hypoplasia of the spinal cord, with a reduction in its diameter, involving either the entire length of the cord, or mainly the upper dorsal and cervical regions. In some cases the cerebellum is the seat of the major changes and if so the syndrome is likely to be classed as hereditary cerebellar ataxia, to which Friedreich's disease is closely related. As a rule the columns of Goll and Burdach are the first to suffer,

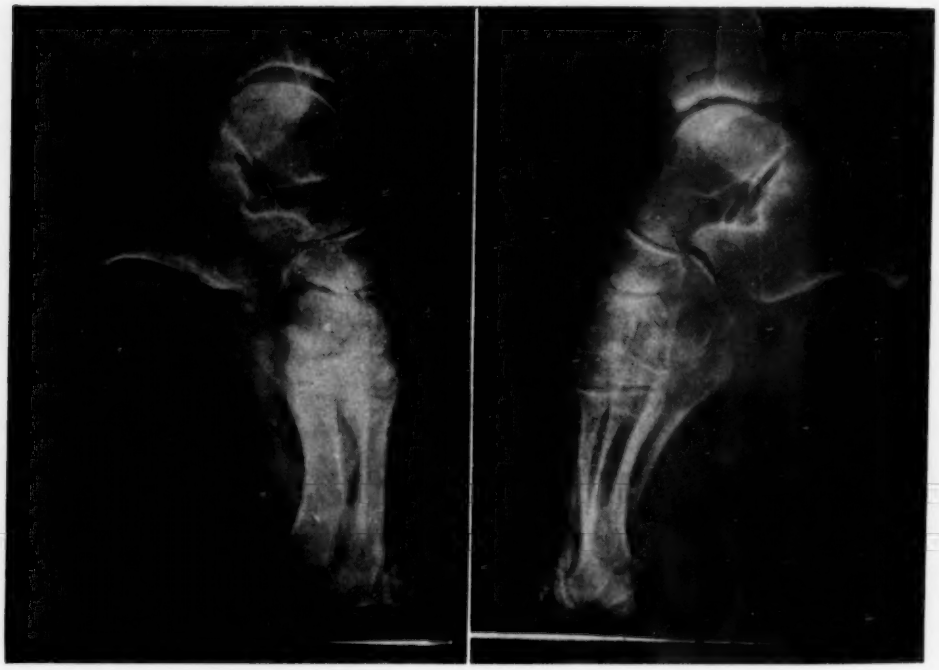

FIG. 4. Roentgen-rays of both feet showing the weight bearing lines.

followed by the pyramidal tracts, columns of Clark, sometimes the ascending cerebellar pathways, and to a variable degree the cerebellum itself. Various secondary manifestations are thickening and adhesion of the pia mater, particularly near the posterior columns, and thickening of the blood vessel walls.[3]

Microscopically there are numerous whorls of neuroglia in the posterior columns, the pyramidal tracts, the cerebellar paths, and the fibers passing from the posterior roots of the spinal cord to the anterior horn cells (part of the simple reflex arc), which are incident to the degeneration in these areas.

CASE REPORT

Mr. H. S., whose history is unreliable as to date of onset, time, and sequence of events, is a bachelor, aged 69, who has had a "high instep" since childhood and pes cavus of the right foot since the age of 24 years. He has been able to work but

during the past 12 years walking has become increasingly difficult, and a gross tremor of the fingers, arms, and head has become much worse. He has also had occasional dizziness.

There is a past history of typhoid fever at the age of 10, gonorrhea at 20, and other infectious diseases at unknown ages. Deafness has been evident in the left ear for nine years. Negative Wassermann and Kahn tests were obtained eight years ago.

The family history includes no known cases of paralysis and none of pes cavus, though he does not "know or remember his parents well."

Physical examination revealed an elderly man weighing 200 pounds, with normal color and features. The hair was gray and skin was of normal color and texture. The nose and ears were negative, except for deafness in the left ear. The head was made conspicuous by an almost continuous gross tremor. The pupils were equal and reacted to light and on accommodation. There was no arcus senilis. The eye grounds showed a normal fundus, with moderate tortuosity of the arteries. There was no nystagmus. The mouth was edentulous.

Chest: The lung fields were clear to palpation, auscultation, and percussion.

Heart: The left border of cardiac dullness was nine centimeters to the left of the mid-sternal line. There was no murmur or irregularity in rhythm. Blood pressure: systolic 158, diastolic 90 mm. Hg.

Abdomen: The panniculus was above the level of the thorax. No abnormal masses or tenderness could be found.

The extremities presented a gross continuous tremor of both upper extremities. The hands were of normal appearance. No abnormality was to be found in the thighs. There was a moderate atrophy of the muscles of the right lower leg, less marked on the left, and some fixation about the right ankle. Temperature and pain sensation were retained on every part of the body. Knee jerks were present, equal and active, although it was impossible to obtain the tendoachilles reflexes. Deep tendon pain was unimpaired, but there was a disturbance of the sense of motion and position as evidenced by the positive Romberg sign, and an inability to tell the position of either great toe when manipulated by the examiner. The finger to nose test was fair, and there was no dysdiadokokinesia. The most striking finding in the extremities was a marked bilateral pes cavus with hyperextension of the great toes and plantar flexion of the remaining digits.

Roentgenograms in this case show, in addition to the pes cavus and dorsal displacement of the proximal phalanges, that the weight was shifted directly to the metatarsals and that the calcanei were supported only by raising the heels of the shoes. No bone abnormality was seen to account for fixation of the right ankle.

Summary

Though the details of the history presented in this case are to some extent unreliable, there has been evident ataxia since childhood, and the patient is now incapacitated to the extent that it requires more than half an hour for him to walk a distance of 200 yards. When walking he leaned slightly forward on two canes with both legs straight, and pulled each foot forward as a step was taken.

There is definitely a lesion involving the proprioceptive fibers and also the pyramidal tracts. A characteristic tremor is present. Occasional attacks of dizziness indicate a probable involvement of the cerebellar pathways.

The retention of the knee jerks is unusual but this is observed in some cases of Friedreich's ataxia. The discrepancies in the history can be ascribed to the

inaccuracies of the patient. The characteristic pedal deformities are practically diagnostic.

Diagnosis: Friedreich's ataxia with onset at some time after puberty.

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A CASE OF SPINDLE CELL SARCOMA OF THE BRONCHUS; SUPPLEMENTARY REPORT *

By Otto S. Baum, M.D., Gertrude Silverman, M.D., Rieva Rosh, M.D., and Richard L. Riley, M.D., *New York, N. Y.*

In November 1938 one of us (O. S. B.) reported a case of atelectasis of the right lower and middle lobes due to spindle cell sarcoma of the right main bronchus.[1] The patient has since died, and this brief supplementary report, with a summary of the autopsy findings, is given for the sake of completeness, as well as because of the nature of the terminal illness. A brief summary of the early course of the disease is also given.

The patient, R. Z., was a 32 year old housewife, first admitted to the Second (Cornell) Medical Division of Bellevue Hospital on March 16, 1938. Six weeks prior to entry she had developed a respiratory illness, diagnosed as "pneumonia and pleurisy" by her physician. A persistent low grade fever, cough productive of small amounts of mucoid sputum, sharp right-sided chest pain, and weight loss of 15 pounds characterized the period intervening between the onset and the episode causing admission. This was characterized by more severe right chest pain, nausea, and vomiting. Salient features of the physical examination were marked deviation of the trachea and mediastinum into the right chest, dullness to flatness, absent breath sounds, and preservation of vocal fremitus over the lower two-thirds of the right chest anteriorly and posteriorly. Laboratory findings, including sputum examination for tubercle bacilli, were negative. Bronchoscopic examination showed a mass of friable polypoid tissue completely obstructing the right main bronchus just below the origin of the upper lobe bronchus. Following the removal of tissue for biopsy and suction

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From the Tuberculosis Service, the Department of Pathology, and the Department of Radiation Therapy of Bellevue Hospital, New York City.

an airway was established, aided by the expulsion of a bronchial cast of tissue shortly after bronchoscopy, and the patient reaerated her right middle and lower lobes within 24 hours. Microscopic examination of tissue removed for biopsy and of the bronchial cast showed a spindle cell sarcoma. Bronchoscopy was repeated 13 days after the first bronchoscopy, at which time the tumor was found to arise on the lateral aspect of the right main bronchus, encroaching on the mouth of the upper lobe bronchus, the orifice of which was transformed into a slit. On the following day deep roentgen therapy was started, treatment being given to the anterior, lateral and posterior aspects of the right chest, directing the center of portal over the center of the lesion.

During the subsequent two and one-half years the patient received therapy at the following periods:

March 31 to June 3, 1938	1950 r. units to each portal
March 3 to March 6, 1939	160 r. units to each portal
March 20 to June 20, 1939	2150 r. units to each portal
	1950 r. units right upper lateral chest
November 13 to December 14, 1939	1400 r. units to anterior and posterior right chest
June 14 to July 18, 1940	2000 r. units to anterior and posterior right chest
September 20 to October 4, 1940	500 r. units directing through right supraclavicular area

Factors used: 200 K.V., 20 ma., 50 cm., STD, 9×12 or 10×15 portal, 0.5 cu. and 1 al. filter output, r. per minute 200 r. given to each area at a time, and one area treated, alternating daily. All measurements made in air. Output 40.5 r. per minute.

Bronchoscopic examinations were performed by Dr. Maxwell Ryan at intervals of approximately three months. In May 1938 the tumor had practically disappeared; only a very small tag of tissue jutted out just below the opening of the right upper lobe bronchus, which was widely patent. This tag of tissue was removed by forceps. In August 1938 there was no visible lesion in the bronchus. In February 1939 there was elevation of the mucosa at the previous site of the tumor, and microscopic examination showed submucosal recurrence of the spindle cell sarcoma. At this time she was admitted to the Tuberculosis Service of Bellevue Hospital for consideration of total pneumonectomy. This was decided against because of the proximity of the neoplasm to the carina, and the patient was referred to the Radiation Therapy Service for further treatment. The sputum at this time was negative for tubercle bacilli.

Roentgen-ray films between March 1938 and August 1939 were considered normal. Beginning August 3, 1939, abnormal findings were noted, consisting of mixed soft and fibrotic infiltration extending from the right hilum into the second anterior interspace, localized by lateral views in the base of the right upper lobe. Subsequent films showed increasing infiltration of the same character, with involvement in the area behind the first anterior intercostal space, where questionable rarefaction was observed. Some retraction of the upper mediastinum into the right chest was first noted in the film of June 6, 1940; on August 16, 1940, nodular deposits were present in the periphery of the right second interspace.

The first abnormal findings in the chest roentgenogram coincided with the onset of a dry hacking cough, associated with occasional sensations of tightness in the chest. Because bronchoscopy in November 1939 showed a small amount of friable tissue at the mouth of the upper lobe bronchus, which bled easily when touched, it was believed that another recurrence had taken place and that the shadows noted in the chest film were due in part to the neoplasm and in part to postradiation fibrosis. Further deep therapy was given cautiously.

During the following year the patient was troubled by a spasmodic unproductive cough and moderate weight loss. Because of these symptoms and of extension of

the process as indicated by roentgen-ray examination a further course of therapy was begun in June 1940.

The patient's final admission to Bellevue was on August 29, 1940, when she gave a history of chills and fever up to 104° F. for the preceding two weeks, associated with further weight loss, night sweats, and increasing sputum which at first had been mucoid but later assumed a purulent character. Physical examination on admission showed a postradiation induration over the anterior, lateral and posterior aspects of the right chest, and dullness and intense bronchial breath sounds with many coarse râles over the region of the right upper lobe. The patient's temperature varied between 101 and 105° F., and was unaffected by two courses of sulfapyridine and sulfadiazine respectively. Bronchoscopic examination on September 11, 1940, showed retraction of the upper lobe bronchus toward the right. At the posterior proximal border of the mouth of the upper lobe bronchus there was a small spongy mass which bled easily. The mouth of the upper lobe bronchus was patent, but there was relatively little air exchange. Microscopic examination of the spongy mass showed only blood clot. The sputum on September 10, 1940, was negative for tubercle bacilli on direct smear. The white blood count fluctuated between 8,000 and 9,100, with 92 per cent polymorphonuclear leukocytes, predominantly young forms. Sputum culture showed the presence of *Staphylococcus aureus*, *Streptococcus viridans*, and *Micrococcus catarrhalis*. Blood culture was negative. Roentgen-ray examination of the chest showed signs of consolidation of the right upper lung field, a large cavity in the first anterior interspace medially, and a soft patchy nodular infiltration in the third anterior interspace.

It was felt that the patient had developed a suppurative pneumonia of the right upper lobe secondary to the bronchial neoplasm, and she was transferred from the Second (Cornell) Medical Service to the Tuberculosis Service for palliative drainage of what was thought to be an abscess of the upper lobe. She had become hoarse during her hospital stay, and laryngoscopy on October 11, 1940, showed abductor paralysis of the left vocal cord, interpreted as due to a mediastinal lesion involving the left recurrent laryngeal nerve. Radiation therapy had been given on five occasions on this admission, 100 r. units being given to the right supraclavicular area each time.

It was a suprise when sputum examination revealed innumerable acid-fast bacilli in the smear, confirmed by several subsequent examinations. An artificial pneumothorax was induced on the right but was abandoned when the upper lobe was found to be densely adherent. The irregular fever persisted, ranging between 102 and 104° F., and the patient rapidly became weaker. Roentgen-ray and physical examination showed evidence of a massive exudative spread into the left lung. For the week prior to death the patient raised increasing amounts of fluid purulent sputum, which now had a foul odor. Death occurred on November 2, 1940, two years and eight months after the first admission to Bellevue Hospital.

Postmortem Examination (Dr. Silverman). The significant autopsy findings were as follows:

Macroscopic: The skin over the right thorax showed diffuse brownish pigmentation. The marrow of the ribs was pale and firm, particularly on the right side. The right lung was adherent to the chest wall over the upper two-thirds, whereas the lower one-third was collapsed by pneumothorax. There were approximately 100 c.c. of clear fluid in the right pleural cavity, and 200 c.c. of serofibrinous fluid in the left pleural cavity. In the anterior superior mediastinum there was an irregular piece of red tissue 3 by 3 by ½ cm. in size, apparently a thymic remnant. The left recurrent laryngeal nerve was free throughout its mediastinal course. The mucous membrane of the trachea and of both main bronchi was fiery red and somewhat thickened. The walls of the right main bronchus and its upper lobe branch were more granular than the rest, but no constriction or ulceration was noted. At the point of bifurcation of the right

upper and lower lobe bronchi, that is, at the site of the original neoplasm, there was a minute firm nodule. No other evidence of neoplasm was noted. The right upper lobe was composed mainly of a single large irregular cavity, with poorly defined, collapsed walls, containing greenish foul-smelling grumous material, which communicated freely with the lumen of the upper lobe bronchus. There were extensive nodular deposits, 2 to 6 mm. in diameter, with evidence of caseation, throughout all the other lobes. In addition there was massive consolidation of the upper portion of the left lower lobe, having the appearance of an acute tuberculous pneumonia. The pulmonary artery going to the right upper lobe was completely occluded by a firmly attached, pinkish-gray thrombus. There were a number of small black mediastinal lymph nodes.

Microscopic: The nodule at the bifurcation of the upper and lower lobe bronchi on the right was made up of bundles of apparently fibrous tissue running in various directions, abutting at its base against necrotic tuberculous tissue and older fibrous tissue with a round cell infiltration. Deep-lying vessels showed calcification in their walls (radiation therapy changes).

The lining of the trachea and main bronchi throughout showed metaplasia into squamous epithelium and extensive caseous and proliferative tuberculosis. The wall of the right upper lobe cavity was made up of necrotic lung tissue with no delimiting granulation or fibrous tissue or adjacent inflammatory reaction. There was almost complete necrosis of all adjacent lung tissue. The small arteries showed inflammatory infiltration and destruction of their walls and recent thromboses in their lumina. The wall of the main upper lobe branch of the pulmonary artery was necrotic, probably the result of direct extension of tuberculous caseation from a partly epithelialized bronchus. Sections throughout the remainder of both lungs showed extensive caseous tuberculosis. Lymph nodes below the carina showed proliferative tuberculosis. Section of the tissue from the anterior superior mediastinum showed striated muscle, loose fibrofatty tissue, and lymphoid tissue. The latter showed old hyalinized foci, in places diffuse fibrosis, and isolated epithelioid tubercles with some necrosis and giant cell formation. In the loose fatty tissue there was a single calcified body (old Hassal's corpuscle?) and perivascular cellular infiltration of large lymphocytes and fibroblasts, inflammatory in character. The liver showed evidence of terminal hematogenous generalization of the tuberculosis, there being small proliferative tubercles scattered through the section. Sections of the recurrent laryngeal nerve, using trichrome, Loyez, neuroglia, and Sudan IV stains, showed no inflammatory or degenerative changes.

Discussion

In our previous review of the literature on sarcoma of the lung we referred to the well known fact that the histological appearances of inflammatory lesions and overgrowths of reparative tissue may simulate round and spindle cell sarcomata. With this in mind we reviewed the sections of the two bronchoscopic biopsies and of the material coughed up following the first bronchoscopy, and found no evidence pointing to such an etiology, all the sections showing spindle cell sarcoma with no subjacent or adjacent foci of tuberculosis. There remains the remote possibility that there was a tuberculous focus in adjacent pulmonary parenchyma or in one of the peribronchial lymph nodes responsible for the abnormal overgrowth of fibrous tissue. That this is extremely unlikely is attested by the lack of any similar microscopic findings reported in the literature. The usual finding in the event that an active tuberculous focus encroaches on a bronchus consists at first of a non-specific, later of a specific inflammatory

reaction in the bronchial wall, neither of which obtained here. It may be concluded, therefore, that the neoplastic process was not derived from a tuberculous focus, either in the adjacent pulmonary parenchyma, bronchus, or lymph node.

We may then assume that this is a true case of spindle cell sarcoma, arising probably in the bronchial submucosa, and apparently cured by deep roentgen therapy. That radiation reached the area of the neoplasm is evidenced by the "postradiation" calcific changes in the walls of adjacent vessels. The only remaining evidence of a previously existing growth was the fibromatous nodule at the site of the former tumor.

The part played in this case by tuberculosis can be reconstructed on the basis of known pathological changes, and probable pathogenesis. The cavity, which was first noted on the final admission, was probably an uncomplicated tuberculous lesion. The assumption that it was an abscess, secondary to bronchial obstruction, and that the abscess in turn eroded a tuberculous focus, is unlikely, since there was no evidence of bronchial obstruction either at bronchoscopy or at postmortem examination. Furthermore, until the last week, the sputum did not show the foulness usually associated with this type of abscess. The autopsy did reveal, however, a tuberculous endobronchitis throughout the bronchi leading to the cavity, suggesting that the inflammatory disease of the bronchi was secondary to parenchymal tuberculosis.

The terminal gangrene of the right upper lobe was most probably due to thrombosis of the upper lobe branch of the right pulmonary artery, and the fetidity of the sputum resulted from subsequent infection of the open cavity with anaerobic organisms. This mechanism is well recognized as accounting for occasional cases of putrid infection of a preëxisting tuberculous cavity.

In order to explain the rapidly progressive tuberculosis we are inclined to suspect that the necessarily heavy dosage of roentgen-rays played a part. It is known that the activity of exudative tuberculous lesions is increased, and that caseation is accelerated by roentgen therapy. In this case, before accelerating caseation of the active lesion, irradiation may have either activated a quiescent tuberculous focus, or rendered the pulmonary parenchyma more vulnerable to tuberculous infection.

We are unable to explain the recurrent laryngeal nerve palsy, which was noted independently by two observers.

Summary

We have presented a case of spindle cell sarcoma of the bronchus, treated and apparently cured by intensive deep roentgen therapy, in which death supervened as a result of rapidly progressive pulmonary tuberculosis, complicated terminally by pulmonary gangrene due to thrombosis of the pulmonary artery.

We wish to express our gratitude to Drs. John H. Richards, J. Burns Amberson, Jr., and Douglas Symmers for suggestions and criticisms aiding the preparation of this report.

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EDITORIAL

THE RÔLE OF MONONUCLEAR PHAGOCYTES IN IMMUNITY TO TUBERCULOSIS

IMMUNITY to tuberculous infection differs in many ways from that occurring in infections with most of the ordinary pathogenic bacteria. In the laboratory animals which have been most carefully studied and probably in man any notable degree of resistance seems to depend upon the presence of living tubercle bacilli in the body tissues. If a normal rabbit or guinea pig is inoculated locally with a suitable dose of a pathogenic strain, the animals show but little resistance to the infection, the organisms multiply freely and the infection becomes disseminated. If, however, such an injection is made into an animal previously infected, a marked inflammatory reaction promptly occurs in the tissues about the site of injection, which tends to prevent multiplication of the bacilli and to restrict their spread.

The mechanism by which this immunity to reinfection is brought about has not been entirely elucidated. Attempts to demonstrate significant activity in the serum of such animals have failed for the most part. Antibodies in relatively low titer have been demonstrated, but such sera do not show direct bactericidal activity in vitro, and they have not shown appreciable protective or curative power. It has therefore been believed that an altered activity of the tissue cells must play an essential part in the process. Extensive histological and cytological studies have indicated that the mononuclear phagocytes are largely concerned in the defense reaction.

In earlier experiments Lurie [1] demonstrated that the inoculation of immune (that is, previously infected) animals results in a much more marked and prompt mobilization of mononuclear phagocytes than occurs in a normal animal. Mononuclear phagocytes obtained from immune animals by intraperitoneal injections of sterile irritants like aleuronat showed a greater capacity to phagocyte tubercle bacilli in vitro than did those from normal animals, regardless of whether normal serum or immune serum was added to the mixture. However, they also showed an increased capacity to take up carbon particles and staphylococci, a phenomenon which can not be ascribed to a specific immune reaction. Furthermore, these "immune" cells showed some morphological differences from those of normal animals. They were often larger, contained more abundant cytoplasm, more numerous and larger vacuoles stainable by neutral red in supravital preparations, and larger pseudopodia; and cells showing mitotic or amitotic division were more numerous. A similar increased outpouring of phagocytes in the tuberculous animal was observed also after injections of nonspecific irritants.

[1] LURIE, M. B.: Studies on the mechanism of immunity in tuberculosis. The mobilization of mononuclear phagocytes in normal and immunized animals and their relative capacities for division and phagocytosis, Jr. Exper. Med., 1939, lxix, 579–605.

Such observations suggested a heightened physiological activity on the part of the sensitized animal rather than a manifestation of specific immunity. However, the tubercle bacilli failed to multiply in phagocytes from immune animals, whereas they did so actively in cells of normal animals.

Attempts to determine the parts played by serum antibodies, on the one hand, and by tissue changes, on the other, in this inhibition of growth heretofore have not led to conclusive results. In tissue cultures in vitro, mononuclear phagocytes from immune animals have shown no greater inhibitory effect upon the multiplication of tubercle bacilli than those from normal animals.[2] Manifestly, however, it is difficult in tissue cultures to maintain conditions comparable to those in the animal body for a considerable period of time, and such negative results could not be regarded as conclusive.

In recent ingenious experiments Lurie[3] has furnished new and more direct proof of the rôle played by these cells in the defense process. He utilized the anterior chamber of the eye of albino rabbits as a culture medium for the phagocytes, inoculating into one eye, for example, cells from an immune animal, and into the other eye, cells from a normal animal as a control.

He first obtained monocytes which had taken up tubercle bacilli in vivo, by injecting normal and immune rabbits subcutaneously with a virulent culture. Two days later he excised the regional lymph nodes and cut them into small fragments which were washed in sterile Tyrode's solution and injected into the anterior chamber of the eyes of a normal rabbit. He also used suspensions of bone marrow from both normal and immune animals which had previously received intravenous injections of tubercle bacilli. After about 14 days the animals were killed and the eyes examined. By histological and cultural studies he demonstrated that the number of living tubercle bacilli in the cells from the normal animal was much greater than in the cells from the immune animal, although the "immune" cells at the time of the inoculation had phagocyted more bacilli than the normal cells. The cells of the immune animal, therefore, markedly inhibited the growth of the tubercle bacilli which they had ingested, as compared with the multiplication of the bacilli in the normal cells. This experiment, however, did not determine whether this activity depended upon a change inherent in the cell itself, or whether it was due to the action of the serum of the immune animal upon the bacilli before their ingestion.

To determine this point, Lurie obtained suspensions of mononuclear phagocytes from both normal and immune rabbits by making intrapleural injections of gum acacia solution. The cells in the resulting exudates were washed to free them as thoroughly as possible of body fluids, and similar suspensions were prepared in citrated salt solution. To such suspensions were

[2] Rich, A. R., and McCurdock, H. A.: Enquiry concerning rôle of allergy, immunity and other factors of importance in pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, xliv, 273–422.

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added serum, either from a normal or an immune animal, as required by the experiment, and a suitable suspension of living virulent tubercle bacilli. After a preliminary incubation to permit phagocytosis to take place the supernatant fluid was removed by brief centrifugalization to get rid of the free bacilli, and replaced by the same type of serum originally present in the mixture. A portion was then inoculated into the anterior chamber of the eye of a normal rabbit, and after two to three weeks the eyes were examined as in the previous experiment.

In this way Lurie compared first, the fate of tubercle bacilli when phagocyted by normal cells in the presence of normal serum, with that when immune serum was used; second, the activity of cells from a normal animal with that of cells from an immune animal when both were suspended in normal serum; and third, when both were suspended in immune serum. The results as described were clear cut. Cells from an immune animal regularly inhibited the growth of the ingested tubercle bacilli, regardless of whether they were suspended in normal serum or in immune serum. On the other hand, under the conditions of the experiment, immune serum did not impart any constant or significant inhibitory activity to normal phagocytes.

These experiments do not exclude the possibility that serum antibodies may contribute to the body's defense from tuberculosis. It is probable that they do so. Earlier experiments of the same investigator [4] showed that if tubercle bacilli were placed in bags impregnated with collodion into which phagocytes could not penetrate, and if the bag was implanted into the peritoneal cavity of a tuberculous animal, multiplication of the organisms was inhibited. When implanted into a normal animal, however, extensive multiplication took place.

The work does demonstrate, however, that the resistance of a tuberculous animal to reinfection depends upon an increased capacity of the phagocytes to destroy or inhibit the growth of the organisms. This change appears to be inherent in the cell itself, and it does not depend upon the presence of immune bodies in the serum or upon the organ environment in which the cells grow.

[4] LURIE, M. B.: Studies on the mechanism of the immunity in tuberculosis. The rôle of extracellular factors and local immunity in the fixation and inhibition of growth of tubercle bacilli, Jr. Exper. Med., 1939, lxix, 555–578.

REVIEWS

Clinical Hematology. By MAXWELL M. WINTROBE, M.D., Ph.D. 792 pages; 24 × 15 cm. Lea & Febiger, Philadelphia. 1942. Price, $10.00.

This volume represents an excellent contribution to the field of hematology. Written by an eminent authority on the subject, the material is covered in an authoritative and lucid manner. Fundamental data concerning the constituents of the blood are fully presented. The blood dyscrasias as well as certain tumor-like conditions involving the blood-forming organs are thoroughly covered. The subject matter is completely documented as evidenced by a bibliography of some twenty-four hundred references many of which are current. Throughout the book discussions of hematological technics are incorporated in chapters of which they logically form a part. Selection of technics has usually been done on the basis of the personal experience of the author. In the main the technics are well chosen. The illustrations, graphs, and charts are of uniformly high quality. This volume can be unreservedly recommended to all persons interested in hematology.

M. S. S.

The Treatment of Burns. By A. B. WALLACE, M.B., F.R.C.S.Ed., M.Sc. (McGill). 113 pages; 17 × 11 cm. Oxford University Press, New York City. 1941. Price, $1.50.

This publication, one of the Oxford War Manuals, is a comprehensive and simply written work, but the reviewer feels that its style may convey to the reader an underestimation of the extent of care that burns require.

The author stresses the absolute importance of shock therapy first, reviews fully the varied types of local treatments, and presses the issue of early skin grafting. These comprise, in essence, the major points in the handling of such patients, particularly in war. However, two important points which should be stressed are that under no circumstances should a general anesthetic be given to a burn patient in shock and that, in the main, most cases can be cleaned gently and thoroughly without anesthesia. Dr. Wallace also stresses extraneous heat in shock; this, however, should be used with extreme discretion so as not to break down nature's protective vasoconstrictor mechanism. These facts are important even in the streamlined treatments of wartime.

Lastly, Dr. Wallace's portrayal of "acute toxemia" is very poor and is not at all in agreement with the concepts of liver insufficiency or hepatorenal syndrome cited in the literature on burns or as exemplified by burns of 50 per cent or more as seen by the reviewer.

Nevertheless, this book should serve as a refresher text and should acquaint the novice with the intricate problem of burns.

C. M. R.

The Physiology of the Kidney. By HOMER W. SMITH, A.B., Sc.D., M.S.(Hon.). 310 pages; 22.5 × 15 cm. Oxford University Press, New York City. 1937. Price, $4.50.

This book is an adequate, detailed treatise on the physiology of the kidney. The author has been most thorough and complete in his discussion of a rather complex and lengthy subject.

The book is logically arranged, with a discussion of the anatomy of the kidney and the theories of renal function in the first chapters. The portion of the book devoted to the renal clearance of inulin, phenol red, and similar subjects is most adequate, and is enchanced by generous reference to the original works. These

subjects are brought up to date, and should prove of value to those interested in this topic.

The book is too detailed to be of practical value to the clinician, but will be a real asset to the student of physiology, and particularly those interested in physiological research and its allied fields.

W. K. D.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Standard Nomenclature of Disease and Standard Nomenclature of Operations. Edited by EDWIN P. JORDAN, M.D. 1022 pages; 19.5 × 12.5 cm. 1942. American Medical Association, Chicago.

Nutrition and the War. Second Edition. By GEOFFREY BOURNE, D.Sc. 148 pages; 19 × 13 cm. 1942. The Macmillan Company, New York. Price, $1.50.

Central Autonomic Regulations in Health and Disease. By HEYMEN R. MILLER, M.D. Introduction by JOHN F. FULTON, M.D. 430 pages; 23.5 × 16 cm. 1942. Grune and Stratton, Inc., New York. Price, $5.50.

Starling's Principles of Human Physiology. Eighth Edition. Edited and revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D.(B'ham). Chapters on the Special Senses revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S. 1247 pages; 24.5 × 16 cm. 1942. Lea and Febiger, Philadelphia. Price, $10.00.

War Medicine—A Symposium. Editor: WINFIELD SCOTT PUGH, M.D., Commander (M.C.) U.S.N. retired. Associate Editor: EDWARD PODOLSKY, M.D. Technical Editor: DAGOBERT D. RUNES, Ph.G. 525 pages; 23.5 × 15.5 cm. 1942. Philosophical Library, Inc., New York. Price, $7.50.

Psychotherapy in Medical Practice. By MAURICE LEVINE, M.D. 320 pages; 22 × 15 cm. 1942. The Macmillan Company, New York. Price, $3.50.

Advances in Internal Medicine. Vol. 1. Editor: J. MURRAY STEELE, M.D. 292 pages; 23.5 × 15.5 cm. 1942. Interscience Publishers, Inc., New York. Price, $4.50.

Emergency Care. By MARIE A. WOODERS, B.S., R.N., and DONALD A. CURTIS, M.D. 560 pages; 22.5 × 15.5 cm. 1942. F. A. Davis Co., Philadelphia. Price, $3.50.

Synopsis of Pathology. By W. A. D. ANDERSON, M.A., M.D. 661 pages; 20 × 13 cm. 1942. C. V. Mosby Co., St. Louis. Price, $6.00.

Shock. Its Dynamics, Occurrence and Management. By VIRGIL H. MOON, A.B., M.Sc., M.D. 324 pages; 24 × 15.5 cm. 1942. Lea and Febiger, Philadelphia. Price, $4.50.

JOURNAL:

Clinics, June 1942 issue, Vol. I, No. 1. Edited by GEORGE MORRIS PIERSOL, M.D. 264 pages; 23 × 15.5 cm. Published bimonthly by J. B. Lippincott Co., Philadelphia. Price, $12.00 per year.

COLLEGE NEWS NOTES

SUPPLEMENTARY LIST OF MEMBERS OF THE COLLEGE ON ACTIVE MILITARY DUTY

In the July and September, 1942, issues of this journal there appeared a list of the Fellows and Associates of the American College of Physicians who were on active duty with the armed forces of their country. Since the publication of these lists the following members of the College have also been reported on active duty:

Frank M. Adams
Harry A. Alexander

Gerald S. Backenstoe
Fred E. Ball, Jr.
Joseph C. Bell
Murray Benson
L. Minor Blackford
J. Lewis Blanton
James L. Borland
Clarence H. Boswell
Burdette J. Buck
Aaron L. Burger
Paul A. Burgeson
William C. Buschemeyer
M. Paul Byerly

Eric M. Chew
T. Sterling Claiborne
Hunt Cleveland
Henry L. Cooper
Linn F. Cooper
Erle B. Craven, Jr.

William M. Donovan
Edgar Durbin

Clarence W. Erickson
A. Carlton Ernstene
George F. Evans

James O. Finney
Russell A. Flack
Harry T. Foley, II
Carl H. Fortune
Saverio C. Franco
Paul K. French
Richard D. Friedlander

Clarence L. Gardner, Jr.
Lee P. Gay
William R. Gibson
Robert W. Gordon
J. Richard Gott, Jr.

Henry H. Haft
Ian B. Hamilton
Paul V. Hamilton
J. Fletcher Hanson
Seale Harris, Jr.
Francis J. Heringhaus
Frederick K. Herpel
Howard E. Heyer
Charles S. Higley
Donald A. Hirsch
J. Morris Horn
Arthur T. Hurst

Donald W. Ingham

Clyde R. Jensen
Alf C. Johnson
Allen S. Johnson

Harry M. Kandel
William K. Keller
Archibald D. Kennedy
Russell W. Kerr
Boyd G. King
Jack D. Kirshbaum
Elmer E. Kottke

Louis H. Landay
Herman A. Lawson
Howard J. Lee
Howard P. Lewis
Joe H. Little

H. Foor Machlan
Lorenzo D. Massey
Fred Mathers
Arthur C. McCarty
Richard F. McLaughlin
James Bowron McLester

Samuel Millman
Flavius D. Mohle
Robert G. Murphy

Robert J. Needles
John Noll, Jr.
F. Garm Norbury
Thomas O. Nuzum

Kenneth A. Owen

Hubert M. Parker
Theodore J. Pfeffer

Warren W. Quillian

Richard Reeser, Jr.
Donald H. Root
Bernard D. Rosenak
Louis Rosenbaum
E. Driver Rowland
Sloan G. Stewart
Merritt H. Stiles
Arthur G. Sullivan
Frederick C. Swartz

William G. Talmage
R. Henry Temple
David S. Traub
William H. Trimble

Thomas V. Urmy

Theodore R. Van Dellen
Walter L. Voegtlin

Joe E. Walker
Oliver W. Welch
William G. Weston
Edward E. Woldman
Richard H. Wood
Irving S. Wright

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Blair Holcomb,F.A.C.P., Portland, Ore.—"A Diebetic Notebook for Use of the Patient";
Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn.—"Man's Greatest Victory Over Tuberculosis";
Dr. Lee Douglas van Antwerp, F.A.C.P., Meriden, Conn.—"The History of Alpha Kappa Kappa."

Reprints

Dr. Morris M. Banowitch, F.A.C.P., Brooklyn, N. Y.—2 reprints;
Dr. Maurice C. Barnes (Associate), Waco, Tex.—4 reprints;
Dr. Archibald A. Barron, F.A.C.P., Charlotte, N. C.—1 reprint;
Dr. Clough Turrill Burnett, F.A.C.P., Denver, Colo.—2 reprints;
William E. Costolow, F.A.C.P., Commander, (MC), U. S. Navy—2 reprints;
Dr. Ralph L. Drake, F.A.C.P., Wichita, Kan.—1 reprint;
Dr. Reginald Campbell Edson (Associate), West Hartford, Conn.—1 reprint;
Dr. Robert H. Flinn (Associate), Bethesda, Md.—1 reprint;
Dr. Aaron Arnold Karan (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—6 reprints;
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—1 reprint;
R. Bruce Logue (Associate), Lieutenant, (MC), U. S. Army—1 reprint;
Horace P. Marvin, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Samuel Millman (Associate), Major, (MC), U. S. Army—2 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—4 reprints;

Dr. F. B. Peck, F.A.C.P., Indianapolis, Ind.—7 reprints;
Dr. C. P. Rhoads, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N.Y.—1 reprint;
Pat A. Tuckwiller, F.A.C.P., Major, (MC), U. S. Army—1 reprint.

At the annual meeting of the American College of Chest Physicians, held in Atlantic City, N. J., June 6–8, 1942, Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., was inducted into the Presidency and Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn., was named President-Elect. Other officers elected at this meeting were Dr. George G. Ornstein, F.A.C.P., New York, N. Y., First Vice President, and Dr. Joseph C. Placak, F.A.C.P., Cleveland, Ohio, Chairman of the Board of Regents. Shelley U. Marietta, F.A.C.P., Brigadier General, (MC), U. S. Army, was elected Governor for the U. S. Army Medical Corps and Robert E. Duncan, F.A.C.P., Commander, (MC), U. S. Navy, was elected Governor for the U. S. Navy Medical Corps.

Dr. Salvatore Lojacono, F.A.C.P., Jackson, Mich., was recently elected President of the Michigan Trudeau Society.

Dr. John C. White, F.A.C.P., New Britain, Conn., retired from the private practice of internal medicine and became the Medical Director of the New Britain General Hospital on September 1, 1942.

At a joint meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, September 23, 1942, Dr. Mahlon Ashford, F.A.C.P., New York, N. Y., spoke on "Coördination of Medical Society Activities." Dr. Louis H. Clerf, F.A.C.P., Philadelphia, addressed the meeting as the retiring President.

Dr. Julius H. Hess, F.A.C.P., Chicago, Ill., was recently appointed a member of the Committee on Youth and Welfare of the Illinois State Council of Defense by the Governor of Illinois.

On July 2, 1942, Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., gave a Mayo Foundation Lecture in Rochester, Minn., on "The Newer Knowledge of Nutrition—How Much of It Is Knowledge?"

Dr. Frank C. Hodges, F.A.C.P., Huntington, W. Va., was recently named President-Elect of the Ohio Society of Pathologists.

Dr. Horace B. Anderson, F.A.C.P., Johnstown, Pa., spoke on "Plasma Banks" at a meeting of the Eleventh Councilor District of the Medical Society of Pennsylvania in Somerset, July 16. At this meeting Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Secretary of the Medical Society of the State of Pennsylvania, presented a fifty year testimonial certificate to Dr. Harry J. Bell, F.A.C.P., Dawson.

The 101st Annual Meeting of the State Medical Society of Wisconsin was held in Milwaukee, September 14–16. Among the speakers were:

Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn.—"Diagnosis of Pathologic Conditions of the Heart";
Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn.—"The Clinical Applications and Complications of the Sulfonamides";
Dr. Edgar A. Hines, Jr., F.A.C.P., Rochester, Minn.—"Normal Range and Hereditary Factors in Hypertension";
Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.—"Actual Clinical Disturbances of the Endocrine Glands";
Dr. Tom D. Spies, F.A.C.P., Cincinnati, Ohio—"Advances in Vitamin Therapy."

Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa., has been named Editor of "Clinics," a new bimonthly journal published by the J. B. Lippincott Company.

Dr. Walter S. Thomas, F.A.C.P., Rochester, N. Y., was named President-Elect of the American Society of Clinical Pathologists at its annual meeting in Philadelphia during June.

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., has been elected President of the American College of Radiology.

Dr. William C. Menninger, F.A.C.P., and Dr. Floyd C. Taggart (Associate) were recently elected members of the Topeka (Kan.) Board of Health.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., discussed physical therapy at a meeting of the Golden-Belt Medical Society in Manhattan, Kan., July 9.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla., has been reëlected Secretary of the Association for the Study of Internal Secretions.

Sanford W. French, F.A.C.P., Colonel, (MC), U. S. Army, spoke on "Medical Care of the Soldiers" and Dr. James E. Paullin, F.A.C.P., President of the College, Atlanta, Ga., spoke on "Medical Care of the Civilian Population in War" at a public lecture sponsored by the Fulton County (Ga.) Medical Society.

Dr. J. Harry Murphy (Associate), Omaha, Nebr., spoke on "Diagnosis and Treatment of Tuberculosis in Childhood" at a meeting of the Lee County (Iowa) Medical Society in Keokuk, June 24.

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Pa., Chairman of the Cancer Commission of the Medical Society of the State of Pennsylvania, spoke on "Use of a Correlating Subject in Science Teaching" at a meeting arranged for high school science teachers by the Philadelphia Cancer Council.

The American Congress of Physical Therapy held its annual session in Pittsburgh, Pa., September 9–12, 1942. Among the speakers were:

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, Pa.—"Refinements in the Treatment of Arthritics Including Physical Therapy";
Christopher J. McLoughlin (Associate), Captain, (MC), U. S. Army—"Physical Therapy in Relation to Military Medicine."

Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, conducted a symposium on "Poliomyelitis."

The Idaho State Medical Association held its annual session in Sun Valley, September 17–19, 1942. Among those who participated were:

Dr. Frank R. Menne, F.A.C.P., Portland, Ore.—"Pathology of Lymph Nodes," "Pathology of the Prostate Gland," and "Pathology of Cancer of the Stomach";
Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore.—"Principles of Chemotherapy," "Differential Diagnosis of Coma," and "Therapeutic Thinking."

On September 1, 1942, Dr. Hugh A. McGuigan, F.A.C.P., retired as Professor of Pharmacology and Therapeutics at the University of Illinois College of Medicine, Chicago.

Dr. Arthur U. Desjardins, F.A.C.P., Rochester, Minn., spoke on "A Group of Persons Whose Skin and Subcutaneous Tissues are Usually Sensitive to Roentgen Rays" at the annual meeting of the American Roentgen Ray Society in Chicago, Ill., September 15–18, 1942.

The Mississippi Valley Trudeau Society and the Mississippi Valley Conference on Tuberculosis held their annual sessions in Chicago, Ill., September 16–18, 1942. Among the speakers at a joint session, September 17, were:

Dr. Oscar A. Sander, F.A.C.P., Milwaukee, Wis.—"Surveying Industrial Personnel";
Dr. Oscar Lotz, F.A.C.P., Milwaukee, Wis.—"The Tuberculin Test and Tuberculosis Control";
Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn.—"County Accreditation for Tuberculosis Control";
Dr. James H. Stygall, F.A.C.P., Indianapolis, Ind.—"Reinfection Tuberculosis in Younger Children."

Dr. Horton C. Hinshaw, F.A.C.P., Rochester, Minn., spoke on "Effect of Reduced Barometric Pressure on Pneumothorax" at a meeting of the Trudeau Society, September 18.

The Wyoming State Medical Society held its 39th Annual Meeting in Cheyenne, August 16–18, 1942. Among the speakers were:

Dr. Thomas D. Cunningham, F.A.C.P., Denver, Colo.—"Virus Pneumonias (So-Called)";
Dr. George E. Baker, F.A.C.P., Casper, Wyo.—"Rocky Mountain Spotted Fever."

The Omaha Mid-West Clinical Society will hold its 10th Annual Assembly in Omaha, Nebr., October 26–30, 1942. One of the sessions of this meeting will be devoted to a symposium on "Newer Concepts Regarding Hypertension and Its Treatment." Among the guest physicians who will speak at this Assembly are:

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.;
Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio;
Dr. Herman H. Riecker, F.A.C.P., Ann Arbor, Mich.;
Dr. Francis E. Senear, F.A.C.P., Chicago, Ill.;
Dr. Irvine H. Page (Associate), Indianapolis, Ind.

Peptic Ulcer Film Available

There is now available for free showings before groups of physicians the first complete movie film on peptic ulcer, in color and with sound track.

The film is entitled "Peptic Ulcer" and was produced under the direction of the Department of Gastro-enterology of the Lahey Clinic of Boston. The American College of Surgeons has awarded its seal of approval to the film.

Running time of the film is 45 minutes, 1600 feet of 16 mm. film, and covers a presentation of the following problems of peptic ulcer: Pathogenesis, diagnosis, treatment, pathology, complications, including obstruction, hemorrhage, and perforation, gastric ulcer, surgery and jejunal ulcer.

Arrangements for a showing of the film may be made by writing to the Professional Service Department of John Wyeth and Brother, Inc., Philadelphia, who will provide projection equipment, screen, film, and operator for medical groups, without charge.

The 15th Annual Graduate Fortnight of the New York Academy of Medicine will be held October 12–23, 1942. The subject of this Fortnight will be "Disorders of the Nervous System." The program will include morning panel discussions, afternoon hospital clinics, evening addresses, and scientific exhibits and demonstrations. Among the Fellows of the College who will speak at the evening sessions are:

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa.—"Military Psychiatry";
Dr. Harold G. Wolff, F.A.C.P., New York, N.Y.—"The Emotions and Disease";
Dr. Walter Freeman, F.A.C.P., Washington, D. C.—"Prefrontal Lobotomy."

Dr. C. C. Burlingame, F.A.C.P., Hartford, Conn., and Forrest M. Harrison, F.A.C.P., Commander, (MC), U. S. Navy, will participate in a panel discussion on

"Psychoneuroses of War." Thomas T. Mackie, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, and Dr. Norman Jolliffe, F.A.C.P., New York, N. Y., will participate in a panel discussion on "The Vitamins in Disorders of the Nervous System." Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., will participate in a panel on "Psychotherapy."

Dr. Arthur F. Chace, F.A.C.P., is Chairman of the Committee on Medical Education of the New York Academy of Medicine; Dr. F. Warner Bishop, F.A.C.P., Chairman of the Committee on Hospital Clinics; Dr. Charles F. Tenney, F.A.C.P., Chairman of the Committee on Panel Discussions, and Dr. Mahlon Ashford, F.A.C.P., is Secretary.

Dr. Ellsworth L. Amidon Elected Acting Governor for Vermont

Dr. Paul K. French, F.A.C.P., College Governor for Vermont, has entered upon active military service as Major in the U. S. Army Medical Corps. Dr. Ellsworth L. Amidon, F.A.C.P., of Burlington, has been elected by the Executive Committee of the Board of Regents as Acting Governor to serve during Major French's absence. Dr. Amidon is Associate Professor of Medicine at the University of Vermont College of Medicine and Medical Director of the Mary Fletcher Hospital. He is a Diplomate of the American Board of Internal Medicine.

The resignation of Dr. Ray M. Balyeat, Oklahoma City, Okla., as a Fellow of the American College of Physicians was accepted by the Board of Regents at St. Paul on April 21, 1942.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., spoke at the New Haven Medical Association on June 17, 1942. His subject was "Clinical Manifestations of Pyruvic Acid Metabolism: I. The Use of B_1 in Uncontrolled Diabetes. II. The Use of B_1 in Protamine Insulin Treated Cases Manifesting Hypoglycemic-like Symptoms at Elevated Blood Sugar Levels."

Regional Meeting of College Members in West Virginia

On July 14, 1942, the Fellows and Associates of the College in West Virginia held a regional meeting at Huntington under the Governorship of Dr. Albert H. Hoge, F.A.C.P., Bluefield.

Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., who was the guest of honor, gave a most interesting discussion on the heat control of the human body and on the various experiments that have been conducted in his laboratory at the Mayo Clinic.

There was also a general discussion by the West Virginia members of the program of the St. Paul Session of the College. This discussion included a detailed report on the action of the Board of Regents concerning the waiver of College dues for members of the College called to active duty with the armed forces of their country. This action of the Board of Regents was very popular and well received.

SPECIAL NOTICES

EXECUTIVE OFFICE OF THE PRESIDENT
NATIONAL RESOURCES PLANNING BOARD
THE SCIENCE COMMITTEE

MEETINGS OF SCIENTIFIC AND LEARNED SOCIETIES

Numerous inquiries are being received from the officers of scientific and learned societies with respect to the possibility or desirability of holding their annual meetings. The Science Committee (advisory to the National Resources Planning Board) which is composed of members designated by the four councils (National Research Council, American Council on Education, American Council of Learned Societies, Social Science Research Council) has thought it desirable to issue the following statement, which has been prepared after consultation with the branches of the Federal Government most concerned. This statement should not, however, be considered an official statement on the part of any branch of the Federal Government.

In view of the fact that the present emergency calls for the greatest mobilization of scientists, scholars, and educators in the history of the United States, it is clear that the societies and associations into which they are organized have an important part in the war effort. This part includes not only direct participation by scientists, technologists, scholars, and others in war activities, but also the discussion of present and future problems and the maintenance of a vigorous intellectual life. There are no fields of knowledge which are not affected, and which have not some contribution to make.

It may safely be assumed, therefore, that the meetings of scientific, scholarly, and educational societies and associations may be so organized as to be in the public interest. It is important, however, that these meetings should be organized in such a way as not to interfere in any way with the actual prosecution of the war.

The Science Committee suggests, therefore, that each society or association should consider the relationship which its field or discipline bears to the war effort, and the contribution that it can make, and that it should plan the program of its meeting with this relation or contribution in view; not overlooking, however, the importance of giving consideration to the post-war period, nor the necessity of maintaining such activities as contribute to a strong national intellectual life.

The Science Committee points out, however, that so far as possible meetings should not be held in or near defense areas, especially the ports and cities of the Atlantic seaboard, and that they should be held on such days of the week as to avoid, as far as possible, week-end (Friday noon to Monday noon) travel. The suggestion is made that some of the large associations may find it advantageous to organize their annual meeting in regional gatherings rather than in a single meeting in one place. It is furthermore suggested that the societies and associations should distribute their meetings among different cities in order to avoid congestion at any one point or along routes of travel.

The Science Committee has been requested to point out the increasing difficulty of handling civilian traffic, the difficulty in securing space and seats, the possibility of late trains and misconnections, and the importance of voluntary curtailment of nonessential travel.

It has further been suggested to the Science Committee that meetings not closely connected with the war effort should be postponed, and that attendance at all meetings should be confined to those whose presence or participation is deemed to be useful. Finally, the Science Committee wishes to point out that the above statement is based upon conditions of transportation that exist at the present time, and

that changes in those conditions may take place and may necessitate radical changes in plans for meetings. Organizers of meetings should accordingly be prepared promptly to make necessary changes in their plans.

EDWIN B. WILSON
Chairman, Science Committee

WASHINGTON, D. C., AUGUST 20, 1942

The Surgeon General of the Army published detailed information concerning policies governing the initial appointment of physicians as medical officers on April 23, 1942. Necessary changes are given wide publicity, at his request, in order that the individual applicants, and all concerned in the procurement of medical officers, may know the status of such appointments.

The current military program provides for a definite number of position vacancies in the different grades. The number of such positions must necessarily determine the promotion of officers already on duty and, in addition, the appointment of new officers from civilian life. Such appointments are limited to qualified physicians required to fill the position vacancies for which no equally well qualified medical officers are available. Such positions calling for an increase in grade should be filled by promotion of those already in the service, insofar as possible, and not by new appointments.

If this policy is not followed, it would definitely penalize a large number of well qualified Lieutenants and Captains already on duty by blocking their promotions which have been earned by hard work. In view of these facts, it has been deemed necessary to raise the standards of training and experience for appointment in grades above that of First Lieutenant.

With this in view, The Surgeon General has announced the following policy which will govern action to be taken on all applications after September 15, 1942:

All appointments will be recommended in the grade of First Lieutenant with the following exceptions:

Captain. 1. Eligible applicants between the ages of 37 and 45 will be considered for appointment in the grade of Captain by reason of their age and general unclassified medical training and experience.

2. Below the age of 37 and *above* the age of 32, *consideration* for appointment in the grade of Captain will be given to applicants who meet all of the following minimum requirements:

a. Graduation from an approved medical school.
b. Internship of not less than one year, preferably of the rotating type.
c. Special training consisting of 3 years' residency in a recognized specialty.
d. An additional period of not less than 2 years of study and/or practice limited to the specialty.

3. Eligible applicants who previously held commissions in the grade of Captain in the Medical Corps (Regular Army, National Guard of the United States, or Officers Reserve Corps) *may be considered* for appointment in that grade provided they have not passed the age of 45 years.

Major. 1. Eligible applicants between the ages of 37 and 55 *may be considered* for appointment under the following conditions:

a. Graduation from an approved school.
b. Internship of not less than one year, preferably of the rotating type.

c. Special training consisting of 3 years' residency in a recognized specialty.

d. An additional period of not less than 7 years of study and/or practice limited to the specialty.

e. The existence of appropriate position vacancies.

f. Additional training of a special nature of value to the military service, in lieu of the above.

2. Applicants previously commissioned as Majors in the Medical Corps (Regular Army, National Guard of the United States, or Officers Reserve Corps) whose training and experience qualify them for appropriate assignments may be *considered* for appointment in the grade of Major provided they have not passed the age of 55.

Lieutenant Colonel and Colonel. In view of the small number of assignment vacancies for individuals of such grade, and the large number of Reserve Officers of these grades who are being called to duty, such appointments will be limited. Wherever possible, promotion of qualified officers on duty will be utilized to fill the position vacancies.

Much misunderstanding has arisen concerning recognition by Specialty Boards and membership in specialty groups. It will be noted that mention is not made of these in the preceding paragraphs. This is due to the variation in requirements of the different Boards and organizations. Membership and recognition are definite factors in determining the professional background of the individual, but are *not* the deciding factors, as so many physicians have been led to believe.

The action of the Grading Board, established by The Surgeon General in his office, is final in tendering initial appointments. Proper consideration must be given such factors as age, position vacancies, the functions of command, and original assignments. All questionable initial grades are decided by this Board. Due to the lack of time, no reconsideration can be given.

There are in the age group 24–45 more than a sufficient number of eligible, qualified physicians to meet the Medical Department requirements. It is upon this age group that the Congress has imposed a definite obligation of military service through the medium of the Selective Service Act. The physicians in this group are ones needed *now* for active duty. The requirements are immediate and imperative. Applicants beyond 45 years may be considered for appoint only if they possess special qualifications for assignment to positions appropriate to the grade of *major* or above.

The Directing Board of the Procurement and Assignment Service of the War Manpower Commission told its State Chairman for Physicians to retain in their present positions full-time and part-time industrial physicians and physicians serving State industrial hygiene bureaus on a full-time basis.

Chairman Paul V. McNutt, of the War Manpower Commission, through Dr. Frank H. Lahey, chairman of the directing board, said in a statement to the state chairmen:

"A serious situation is developing in some states because physicians under 45 years of age who are essential in their present positions as key men in industrial practice are being declared available by State Chairmen or are being approached directly by recruiting boards with instructions to apply for a commission in the Army Medical Corps.

"The Selective Service System and the Surgeons General of the Army and Navy are coöperating with us to keep at their posts the physicians declared to be essential by our State Committees."

Mr. McNutt asked the physicians to be guided by the following criteria, which have been recommended by the Committees on Industrial Health and Medicine and have been approved by the Directing Board:

A physician employed in industry is deemed to be essential when the following conditions exist:

A. Full-time industrial physician.

1. The physician is employed by an industry which is manufacturing war materials exclusively or under priority ratings, and
2. The physician gives his full time to the industry or 40 or more hours weekly, has been so employed for at least two years or is especially trained for that purpose and is carrying on an acceptable health maintenance program, and
3. The physician is performing the functions of a medical director or department head or of a specialist or is the only physician employed.
4. Assistant physicians who perform routine functions under direction, and are employed on a full-time basis, are deemed essential until they can be replaced within a reasonable time (3 to 6 months).

B. Part-time industrial physician.

1. The physician serves part-time two or more industries engaged exclusively in the manufacture of war materials or under priority ratings, provided his total part-time service is the equivalent of 40 or more hours weekly. Note: The physician who serves on call only is not deemed to be essential.

C. The physician serves a State industrial hygiene bureau on a full-time basis.

Chairman Paul V. McNutt of the War Manpower Commission announced the standards by which public health physicians should be considered essential to public health interests and non-available for military duty.

The Procurement and Assignment Service of the War Manpower Commission adopted the standards upon recommendation of its Advisory Committee on Public Health, headed by Dr. Carl Reynolds, State Health Officer for North Carolina.

According to the Procurement and Assignment Service standards, "A physician should be considered essential to civilian public health interests and, therefore, not available for military duty provided he comes within either one of the two following categories:

1. A full-time medical officer in charge of a health service of a governmental unit or administrative district, such as State, district, county, and city.
2. Full-time heads or chiefs of administrative units within a health department. For example: tuberculosis, venereal diseases, maternal hygiene, infant care, epidemiology, vital statistics, etc.

"Methods of health service differ throughout the States; public health problems vary with localities, population densities, and in terms of war industries, military centers, and so forth, which may create special problems where located," said the report of the Advisory Committee on Public Health to the Directing Board of the Procurement and Assignment Service.

"The committee, therefore, does not deem it feasible to submit any specific recommendations for Nation-wide application as to the essentiality of full-time medical officers serving health departments in capacities other than those in the two groups set forth above.

"In view of these facts, this committee recommends that the essential designation of physicians in capacities other than those described above be determined after conference between the administrative chief of the health department concerned and the State chairman of Procurement and Assignment Service.

"Physicians in public health positions, other than those specified in categories 1 and 2, who are under 37 years of age, should expect to be released for military service, except under unusual circumstances, and their places should be taken by older persons.

"Special consideration, however, shall be given to trained health officers who have had two or more years of training and service in public health.

"Furthermore some of these who may not be essential locally may be needed by the U. S. Public Health Service for service elsewhere."

Mr. McNutt praised the patriotic spirit of those who, when remaining at home, performed their medical services willingly and with the attitude that they were doing their equal share in the present crisis.

OBITUARIES

DR. ADAH McMAHAN

Dr. Adah McMahan, Associate of the American College of Physicians since 1925, of La Fayette, Ind., died June 24, 1942, of postoperative shock following cholecystectomy.

Dr. McMahan was born January 12, 1869; received her A.B. degree in 1889 and her A.M. degree in 1893 from Indiana University. She graduated in medicine from the Northwestern Woman's Medical School, Chicago, in 1897. During World War I, she served in France. She was a former President of the Tippecanoe County Medical Society, a member of the Indiana State Medical Society and of the American Public Health Association; also a Fellow of the American Medical Association. She had formerly served as a member of the Indiana State Board of Health and was on the staff of St. Elizabeth and La Fayette Home Hospitals.

Dr. McMahan was highly esteemed personally by members of the profession, who also had a high regard for her work.

DR. CLARENCE M. GRIGSBY

Medicine in the Southwest has lost a staunch and faithful exponent in the passing of Dr. Clarence Manning Grigsby, of Dallas, Texas, who died on June 14, 1942, of hypertensive heart disease and angina.

Dr. Grigsby was born near Homer, Louisiana, October 27, 1868, and graduated in medicine from the College of Physicians and Surgeons in Baltimore in 1893. He pursued postgraduate studies in all of the medical centers in this country, and served as Associate Professor of Medicine and Professor of Medicine, also as Professor of Clinical Medicine, at Baylor University College of Medicine. At his death he was Emeritus Professor of Medicine at Baylor College.

Dr. Grigsby was an ardent supporter of organized medicine, and had served as President of the Dallas County Medical Society and as Chairman of the Sections on Medicine of the Texas State Medical Association and the Southern Medical Association. Many valuable papers were published by Dr. Grigsby. He was a Diplomate of the American Board of Internal Medicine, and since 1921 had been a Fellow of the American College of Physicians, serving the College for many years as Governor for Texas. His host of friends in the American College of Physicians will sorely miss Dr. Grigsby at the annual meetings, very few of which he ever failed to attend. His ready wit and ever-ready story for all occasions endeared him to everyone who was fortunate enough to know him. His interest in the younger men in the profession has been perpetuated by his will, his entire estate being left to build up the Department of Medical History in Baylor University Medical College, which he served so long and well.

The death of Dr. Grigsby will cause deep sorrow to his many friends over the entire country.

M. D. Levy, M.D., F.A.C.P.,
Governor for Texas

DR. MAXIMILIAN JOHN HUBENY

Maximilian John Hubeny, F.A.C.P., F.A.C.R., Chicago, born in Leipzig, Germany, October 12, 1880, of Bohemian parentage; died in Chicago, July 2, 1942, aged 61. While enroute in his automobile to the hospital, he was seized with a sudden, severe cardiac attack and, fully realizing its significance, he induced a service station attendant to chauffeur him the remainder of the way. They reached the Cook County Hospital, but their arrival was almost coincident with his death, due to an acute coronary occlusion.

Heredity endowed him with all the qualifications of a real gentleman, which were augmented by home environment and education. To these were subsequently added those of a scholar and scientist. By nature he possessed a most amiable disposition and personality, characterized by high ideals and unlimited amount of energy.

He received his M.D. degrees from Hahnemann Medical College and Hospital of Chicago in 1906 and from the College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909. As a medical student he was outstanding, justifying a prediction of success and leadership. For a time after graduation, general practice occupied his attention, but very soon he was attracted to roentgenology which was his chosen field during the remainder of his life.

At one time Dr. Hubeny was Roentgenologist at Henrotin Hospital and at the Municipal Tuberculosis Sanitarium (Chicago); since 1936 he had been Director of the X-Ray Department of Cook County Hospital and Professor of Roentgenology and Chairman of the Department at Cook County Graduate School of Medicine. Dr. Hubeny was Secretary of the Section on Radiology of the American Medical Association from 1923 to 1926 and at one time was Editor of the journal, "Radiology," and Associate Editor of the "American Journal of Cancer," "The Italian Journal of Radiology," and the "Cuban Journal of Radiology." In 1931 he was awarded a gold medal by the Radiological Society of North America for research. Dr. Hubeny was a Diplomate of the American Board of Radiology; a member of the American Roentgen Ray Society; a member and past president of the Radiological Society of North America, the Chicago Roentgen Society and the American College of Radiology; a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1920.

His colleagues and friends, those who knew him best, cherish his memory as a tried and trusted friend, always kind, sympathetic and most generous to those in need of his assistance. Mercenary he was not, for this was

foreign to his nature. He will long be remembered and his passing regretted by all who knew him.

FREDERICK TICE, M.D., F.A.C.P.,
Chicago, Ill.

DR. JOSEPHUS PATMAN BOWDOIN

Josephus Patman Bowdoin, Atlanta, Georgia, died on August 7, 1942, at the age of 76. He was stricken at his office and taken to a hospital, where he passed away a few hours later.

Dr. Bowdoin was born in Adairsville, Georgia, on May 7, 1866. He attended Atlanta Medical College (now Emory University School of Medicine) and graduated as valedictorian of his class in 1889. Following his graduation, he returned to Adairsville and practiced medicine in Bartow and surrounding counties for nearly 30 years. During this period he served as president of his county medical society, chairman of the district society and surgeon for many years for the N.C. & St.L. Railroad.

At the beginning of World War I, Dr. Bowdoin volunteered his services and served as a surgeon in the U. S. Public Health Service. Following this, he entered public health work in Georgia as Director of the Division of Venereal Disease Control, acting in that capacity until July, 1939, and of the Division of Child Hygiene. In 1921 he was elected by the State Board of Health as Deputy Commissioner of Health of Georgia.

In 1920 he began to edit the monthly bulletin, "Georgia's Health" and continued to do so until his death. He contributed many articles to medical journals and was author of "Georgia Baby Book," now in its eighth edition.

Outside of the medical profession, Dr. Bowdoin took a large part in fraternal, civic and public affairs, being for many years a member of the Board of Education in Adairsville.

Dr. Bowdoin had been a Fellow of the American College of Physicians since 1929.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia